



Publisher's Disclaimer. E-publishing ahead of print is increasingly important for the rapid dissemination of science. The **Early Access** service lets users access peer-reviewed articles well before print / regular issue publication, significantly reducing the time it takes for critical findings to reach the research community.

These articles are searchable and citable by their DOI (Digital Object Identifier).

The **Monaldi Archives for Chest Disease** is, therefore, e-publishing PDF files of an early version of manuscripts that have undergone a regular peer review and have been accepted for publication, but have not been through the typesetting, pagination and proofreading processes, which may lead to differences between this version and the final one.

The final version of the manuscript will then appear in a regular issue of the journal.

E-publishing of this PDF file has been approved by the authors.

All legal disclaimers applicable to the journal apply to this production process as well.

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:

Ramdani I, Chahed R, Bouazza B. **The effect of azelastine on basal forced expiratory volume in one second in asthmatics: a systematic review and meta-analysis.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2026.4040

Submitted: 11-04-2026

Accepted: 14-10-2026



©The Author(s), 2026

Licensee [PAGEPress](#), Italy

Note: The publisher is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries should be directed to the corresponding author for the article.

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

**The effect of azelastine on basal forced expiratory volume in one second in asthmatics:
a systematic review and meta-analysis**

Idir Ramdani,¹ Rachid Chahed,² Belaid Bouazza^{1,3}

¹Biochemistry, Biomolecules and Inflammation Research Team, Ecology, Biotechnology and Health Lab, Mouloud Mammeri University of Tizi-Ouzou; ²Private Office of Pulmonary Medicine, Tizi-Ouzou; ³Center for Biotechnology Research, Constantine, Algeria

Correspondence: Belaid Bouazza, Biochemistry, Biomolecules and Inflammation Research Team, Ecology, Biotechnology and Health Lab, Mouloud Mammeri University of Tizi-Ouzou, Route de Hasnaoua, 15000 Tizi-Ouzou, Algeria.

Tel.: 213-561980787. E-mail: belaid.bouazza@ummto.dz

Contributions: Belaid Bouazza: study concept. Idir Ramdani, Belaid Bouazza: design of the methodology, screening of databases and data extraction. Idir Ramdani: draft of the first manuscript. Rachid Chahed, Belaid Bouazza: review and editing of the manuscript. All authors revised and approved the final manuscript.

Conflict of interest: the authors have no competing interests to disclose.

Ethics approval and consent to participate: not applicable. This study (meta-analysis) do not involve human subjects thus do not require IRB review or informed consent.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this article.

Acknowledgments: the authors would like to thank Dr Ponniah Selvakumar (Department of Pharmaceutical Sciences, Thomas Jefferson University, Philadelphia, USA) for critically

reading the manuscript.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: the authors report that no generative AI or AI-assisted technologies were used in the research, writing, or preparation of this manuscript.

Abstract

Nearly 5 to 10% of asthmatics show a problematic drug tachyphylaxis, featuring the need for new therapies. Bitter taste receptors (TAS2Rs) are expressed in the airway tract, and their activation leads to multiple antiasthma effects. Azelastine, an antihistaminic drug with a strong bitter taste, is used to treat allergic rhinitis but is frequently prescribed for asthma. The present study aims to evaluate the bronchodilator effect of azelastine in asthmatic patients. We searched PubMed, the Cochrane Library, and Scopus databases from inception to April 1, 2026. Studies investigating the effect of azelastine on baseline forced expiratory volume in one second (FEV1) of asthmatic patients, compared to a placebo, were included. Mean differences between the two arms were calculated using a random effects model. The systematic search retrieved 145 articles, of which 8 met the inclusion criteria. Azelastine improved FEV1 by 7.57% compared to placebo ($p < 0.001$). The heterogeneity was low ($I^2 = 0\%$), and the overall methodological quality of the selected studies was high, except in four studies, where a risk of bias was observed due to deviations from the intended intervention. Meta-regression analysis showed no significant impact of age, sex ratio, and baseline FEV1 on the global effect size ($p > 0.05$). Azelastine treatment improves FEV1 in asthmatic patients. These results support the previously reported bronchodilator benefits of azelastine through TAS2Rs activation. However, more clinical studies are still needed to explore the therapeutic potential of TAS2R-targeted treatments in asthma.

Key words: TAS2R, azelastine, asthma, FEV1, bronchodilation.

Introduction

Asthma is a prevalent airway disease characterized by chronic inflammation, airway remodeling, and episodic reversible airway obstruction [1]. The standard treatment regimen for asthma consists of inhaled glucocorticoids (GC) to manage inflammation, and short or long-acting β 2-agonists (SABA and LABA respectively) to relieve bronchospasm [2]. While these medications control symptoms and improve the quality of life for most asthmatics, there is growing evidence of the need for alternative therapies. Indeed, many asthmatics develop resistance to current treatments, necessitating higher dosage to maintain the control of their symptoms [3]. This may lead to several drug side-effects, including recurrent airway infections and growth impairment in children with glucocorticoid use [4], and cardiovascular abnormalities associated with β 2-agonists [5]. As a consequence, recent reports from the Global Initiative for Asthma (GINA), no longer recommend using SABA alone as a reliever [6].

In recent years, studies have shown the expression and function of bitter taste receptors (TAS2Rs) in airway tissues, including the airway smooth muscle (ASM) [7]. Their activation by TAS2R agonists have been shown to induce a potent relaxation of the ASM both in vitro and in vivo, making the TAS2R as a candidate for a new class of bronchodilators [8]. However, clinical evidence supporting such bronchodilator effect remains weak, as of today no clinical study have assessed whether these findings remain consistent at the clinical level. Azelastine, a potent histamine H1-receptor antagonist mainly used in the treatment of allergic disorders, including rhinitis and conjunctivitis [9,10] is known for its strong bitter taste as a side effect. Interestingly, Ekstedt et al. demonstrated that azelastine relaxes pre-contracted airways in mice by activating TAS2R, independently of its H1-receptor antagonism [11].

The present systematic review and meta-analysis aims to evaluate the effect of azelastine on baseline forced expiratory volume in one second (FEV1) in patients with asthma.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered on the PROSPERO database (registration number: CRD420251048517). The full checklist and protocol for this study are provided in the supplementary data.

Search strategy and study selection

PubMed, the Cochrane Library and Scopus databases were searched from inception to April 01, 2026, to identify clinical studies investigating the effect of azelastine on baseline FEV₁ in patients with asthma, using the following search strategy:

- (azelastine) AND (asthma OR bronchoconstriction) AND (FEV₁ OR lung function OR pulmonary function)

The search was limited to English-language, placebo controlled clinical trials (randomized or non-randomized), with no restriction on participant age, gender or year of publication. For studies reporting time-course or dose-response data, the time-dose combination associated with the maximum FEV₁ improvement was selected for analysis.

We excluded studies that 1) were observational, reviews, conference abstracts, or letters, 2) limited their investigation to the effect of azelastine on airway resistance, or to the protective effect on broncho-provocation, and 3) were limited to the assessment of the effect of azelastine's chronic treatment.

The selection process involved a systematic review of titles, abstracts, and full texts based on pre-defined inclusion/exclusion criteria. Disagreements were resolved by consensus and through discussion. Zotero software was used for reference management.

Outcomes and measures

The primary outcome was the effect of azelastine on baseline FEV₁ expressed as the percentage of the predicted value. The outcome was quantified as the mean difference in change of FEV₁ between the azelastine and placebo groups.

Data extraction

Two reviewers (IR and BB) independently extracted the characteristics and data from the eligible studies. Extracted information included:

Study characteristics: authors, year of publication, study location, sample size, and study design.

Participant characteristics: age range, sex distribution, asthma severity, comorbidities, and concurrent medications.

Intervention details: route of administration, dosage, timing of FEV₁ measurement, and measured outcomes.

Outcome results: mean change in FEV₁ for both groups and associated p-values.

Assessment of risk of bias

The Cochrane risk of bias tool (RoB)-2 tool was used to assess the methodological quality of the included studies. Studies were evaluated for the following domains:

- Bias arising from the randomization process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in the selection of the reported result.

Each domain was rated as having "low risk," "some concerns," or "high risk" of bias.

Data synthesis and analysis

Meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3.3. Mean differences in FEV₁ change between the azelastine and placebo groups were calculated using a random-effects model. Heterogeneity was calculated by the I² statistic, with I² > 50% considered indicative of substantial heterogeneity. Funnel plots and the modified Egger's test were used to evaluate potential publication bias. Sensitivity analysis was performed to assess the robustness of the meta-analysis, based on different criteria, including the effect model, the methodology strength, azelastine dosage, and asthma stage in the studied population.

Results

Study selection

The database search retrieved 145 records. After removing duplicates and screening titles and abstracts, 24 articles were selected for full-text review based on eligibility criteria. Of these, 8 studies were included in the quantitative analysis. A flow diagram summarizing the study selection process is presented in Figure 1.

Characteristics of the selected studies

All eight studies included in the quantitative analysis were randomized controlled trials (RCTs), incorporating a total of 582 patients, of which 290 received azelastine. The trials were conducted in high-income countries, including the United States, England, and Scotland. In all selected studies, azelastine hydrochloride was administered orally in tablet form, and no RCTs evaluating the effect of inhaled azelastine were found in the literature.

However, the RCTs varied in terms of dosage, timing of FEV₁ measurement, and sample size, which ranged from 10 to 232 participants. It should be noted that all the selected studies are somewhat dated (published between 1986 and 1996), which may limit the generalizability of the results. Table 1 summarizes the characteristics of the included trials.

Quality evaluation

The included trials were subjected to risk of bias evaluation. Four studies were assessed as having a low risk of bias across all five domains [12-15]. The remaining four studies showed a high risk of attrition bias, primarily due to patient withdrawals and small sample sizes [16-19]. Figure 2 summarizes the methodological quality and risk of bias across the included studies.

The effect of azelastine on FEV1

All the included studies reported a positive effect of azelastine on FEV1 compared to placebo. The mean difference in FEV1 improvement between azelastine and placebo groups ranged from 5.5% in the study by the Azelastine-Asthma Study Group [15] to 19% in the study by Kemp et al. [12].

When taking the mean change in FEV1 from baseline in the intervention arm alone (pre- to post-intervention), azelastine showed a clinically relevant improvement in four studies [12,14-16], varying from 12.6% to 28.7%, where baseline FEV₁ was below 80% of predicted. In the remaining studies, the mean change in FEV1 ranged from 4.8% to 9.6%, and the mean baseline FEV₁ was above 80%.

As shown in Figure 3, the random-effects model revealed a significant mean difference of 7.57% in favor of azelastine compared to placebo (95% CI = [5.31-9.82], $P < 0.001$). No heterogeneity was observed through the included RCTs ($I^2 = 0\%$). However, the funnel plot (Figure 4) and Egger's test (two tailed, $P = 0.011$), suggested a potential publication bias, mainly driven by the study conducted by Azelastine-Asthma study group [15]. When this study was excluded from the analysis, the global effect size increased to 9.23%, and Egger's test no longer suggested publication bias (two tailed, $P = 0.067$).

Meta-regression analysis

Meta regression analysis showed that baseline characteristics, including age ($Z = -0.12$, $P = 0.901$), male sex ratio ($Z = 0.37$, $P = 0.710$), and baseline FEV1 ($Z = -0.18$, $P = 0.857$), had

no effect on azelastine efficacy. These findings further support the absence of heterogeneity among the included studies. The meta-regression analysis was summarized in *Supplementary Figure 1*.

Sensitivity analysis

The robustness and reliability of the results were evaluated according to different possible confounding factors, including the model, the methodology strength of studies, azelastine dosage, and asthma stage. In addition, the leave-one out analysis was conducted to determine the impact of each individual study on the overall result.

Interestingly, the results of the primary meta-analysis remain consistent after the sensitivity analysis. Indeed, no variable has decreased the pooled results by more than 0.5%. *Supplementary Table 1* and *Supplementary Figure 2* summarize the sensitivity analysis.

Discussion

Bitter taste receptors (TAS2Rs) have emerged as potential targets for asthma treatment. Many TAS2R agonists have demonstrated anti-asthma effects, including bronchodilator, anti-inflammatory, and anti-remodeling effects in vitro. However, clinical evidence of these effects remains limited.

In this study, we evaluated the effect of azelastine, a known TAS2R agonist, on baseline FEV1 in asthmatics. Interestingly, azelastine improved FEV1 by more than 7% compared to the placebo; this result, though modest, remains significant. Meta-regression analysis revealed that this effect was independent of patient age, sex, and baseline FEV₁, suggesting a consistent therapeutic benefit across different subgroups. Moreover, the results remain consistent through the different subgroups in the sensitivity analysis.

Our results were consistent with those from a previous meta-analysis investigating caffeine, another TAS2R agonist, which also reported positive effects on FEV₁ [20]. Moreover, the included studies reported additional benefits of azelastine, including significant improvements in other lung function parameters such as forced vital capacity, peak expiratory flow rate, and forced expiratory flow at 25-75% [12,14,16], as well as reductions in asthma symptoms and medication use [15]. The statistical heterogeneity was found to be low (0%), suggesting minimal variability in treatment effects across the selected studies. This consistency may be attributed to the relative homogeneity of the study populations (Western, English-speaking cohorts) and the methodological similarities across studies, all of which

were RCTs. Hence, this strengthens our findings, but it limits their generalizability, particularly given the small number of studies ($n = 8$) and participants ($n = 582$) included in the analysis.

In four of the eight included studies, the mean FEV₁ improvement in the azelastine group met or exceeded the widely accepted 12% threshold for assessing the reversibility, reaching up to 28.7% in the study by Chervinsky et al. [14]. Interestingly, the mean baseline FEV₁ in these four studies was found to be under 80% of the predicted value, whereas it was above 80% in the four studies where FEV₁ improvement was below 12%. However, this should be cautiously interpreted, as the numerical change in FEV₁ depends on the degree of airflow obstruction; a lower baseline value inflates the improvement (which also contains the placebo effect) [21,22].

Moreover, in the Azelastine-Asthma Group study, azelastine demonstrated a superior effect to albuterol in some patients [15] underlying an important inter-individual difference of the response to azelastine. This variability between studies could not be explained by sociodemographic factors, as confirmed by meta-regression, but reflects a pattern also seen in *in vitro* studies. Indeed, previous experimental work has shown inconsistent bronchodilator responses to TAS2R agonists, with some reporting stronger effects than β_2 -agonists, and others observing weaker responses [8,23]. According to the literature, many TAS2R agonists have demonstrated potent bronchodilation effect, however, the molecular mechanisms were still unknown. Much of the clinical evidence comes from small-scale trials repurposing existing medications with TAS2R activity, such as chloroquine [24] and colchicine [25], for asthma treatment. Recent research has begun to uncover key pathways by which TAS2R activation may exert anti-asthmatic effects, including membrane hyperpolarization [8], inhibition of the myosin light chain 20 phosphorylation [26], or cofilin activation and F-actin severing [27].

Azelastine has long been used as an H₁-receptor antagonist in the treatment of allergic rhinitis, a common comorbidity in asthma [28]. However, a study by Ekstedt et al. [11] demonstrated that its bronchodilator effect is mediated through TAS2R activation rather than H₁ antagonism, cAMP or cGMP pathways, supporting its potential as a TAS2R-targeted therapy. However, this study only hypothesized the involvement of TAS2R by mimicking the bronchodilator effect of chloroquine, and the authors recognized that mice have a weak histamine system, which limits the anti-H₁ activity of azelastine.

At the clinical level, azelastine exerts multiple effects, including H₁-receptor antagonism and anti-leukotriene C₄ activity, both of which are known to be beneficial in asthma management [29]. In fact, azelastine reduces airway hyperresponsiveness through its H₁-receptor antagonism [30]. Moreover, its anti-leukotriene C₄ activity may reduce systemic inflammation, contributing to the long-term benefit of azelastine (up to 28 weeks in some studies) [29,31]. TAS2R activation may contribute as an add-on effect, as the involved pathways are thought to be independent.

On the other hand, TAS2R-induced bronchodilation is independent of the β -adrenergic receptor pathway, suggesting a complementary mechanism. Moreover, TAS2R agonists have shown sustained bronchodilator effects even in the presence of β_2 -agonist tachyphylaxis [32], highlighting their potential role in treating drug-resistant asthma. However, systemic delivery of TAS2R agonists could lead to side effects, as TAS2Rs are expressed in various tissues throughout the body [33]. For this reason, future formulations should prioritize pulmonary delivery via inhalers or nebulizers to maximize efficacy and minimize systemic side effects.

This systematic review and meta-analysis has strengths, particularly, the inclusion of only RCTs and a low level of between-study heterogeneity. Moreover, our study offers the first comprehensive evaluation of the effect of azelastine, a known TAS2R agonist, on baseline FEV₁ in patients with asthma, an effect that was validated by the sensitivity analysis. However, our study has also limitations. First, the small number of studies and participants limits statistical power and may introduce publication bias, especially since the search was restricted to three major databases (PubMed, Scopus and the Cochrane Library). Second, the analysis was limited to English-language publications, potentially omitting relevant studies in other languages. Third, the scope was restricted to the effect of a single dose of azelastine, excluding studies on its chronic effects, since our focus remained on the acute bronchodilator effect of azelastine in asthmatics. Finally, variability in the timing of FEV₁ measurement across studies complicates the interpretation and generalizability of results. Nonetheless, all included trials adhered to robust methodological standards, consistent with CONSORT guidelines.

Conclusions

The present systematic review and meta-analysis identified eight RCTs comparing the effect of azelastine to placebo on FEV₁ in patients with asthma. The pooled results showed a

statistically significant, though modest, bronchodilator effect of azelastine. As a TAS2R agonist, azelastine improved baseline FEV₁ in asthmatic patients compared to placebo. While the overall effect did not meet the threshold for clinical significance, individual studies demonstrated clinically relevant improvements, some even exceeding the effects of albuterol. Our study provides preliminary clinical evidence supporting the bronchodilator potential of TAS2R agonists. Further RCTs are justified to confirm these results and explore the use of TAS2R-targeted therapies, ideally formulated for pulmonary delivery, to reduce systemic side effects and offer new therapeutic options for patients with difficult-to-treat asthma.

References

1. NHLBI. Section 2, definition, pathophysiology and pathogenesis of asthma, and natural history of asthma. In: Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, MD, USA: National Heart, Lung, and Blood Institute (US); 2007.
2. Dubin S, Patak P, Jung D. Update on asthma management guidelines. *Mo Med* 2024;121:364-7.
3. Kamada AK, Leung DY, Szeffler SJ. Steroid resistance in asthma: our current understanding. *Pediatr Pulmonol* 1992;14:180-6.
4. De Filippo M, Clark E, Fillard A, et al. Oral corticosteroids and asthma in children: Practical considerations. *Pediatr Allergy Immunol* 2020;31:43-5.
5. Marques L, Vale N. Salbutamol in the management of asthma: a review. *Int J Mol Sci* 2022;23:14207.
6. Global Initiative for Asthma. GINA report 2024. Available from: <https://ginasthma.org/2024-report/>.
7. Jeruzal-Świątecka J, Fendler W, Pietruszewska W. Clinical role of extraoral bitter taste receptors. *Int J Mol Sci* 2020;21:5156.
8. Deshpande DA, Wang WCH, McIlmoyle EL, et al. Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. *Nat Med* 2010;16:1299-304.
9. Klimek L, Sperl A, Becker S, et al. Current therapeutical strategies for allergic rhinitis. *Expert Opin Pharmacother* 2019;20:83-9.
10. Bielory L, Lien KW, Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs* 2005;65:215-28.

11. Ekstedt S, Kumlien Georén S, Cardell LO. Effects of MP-AzeFlu enhanced by activation of bitter taste receptor TAS2R. *Allergy Asthma Clin Immunol* 2020;16:45.
12. Kemp JP, Meltzer EO, Orgel HA, et al. A dose-response study of the bronchodilator action of azelastine in asthma. *J Allergy Clin Immunol* 1987;79:893-9.
13. Albazzaz MK, Patel KR. Effect of azelastine on bronchoconstriction induced by histamine and leukotriene C4 in patients with extrinsic asthma. *Thorax* 1988;43:306-11.
14. Chervinsky P, Grossman J, Freitag JJ. Duration of action of a single dose of azelastine in patients with chronic asthma. *J Asthma* 1995;32:141-5.
15. An evaluation of the efficacy and safety of azelastine in patients with chronic asthma. Azelastine-Asthma Study Group. *J Allergy Clin Immunol* 1996;97:1218-24.
16. Tinkelman DG, Bucholtz GA, Kemp JP, et al. Evaluation of the safety and efficacy of multiple doses of azelastine to adult patients with bronchial asthma over time. *Am Rev Respir Dis* 1990;141:569-74.
17. Ollier S, Gould CA, Davies RJ. The effect of single and multiple dose therapy with azelastine on the immediate asthmatic response to allergen provocation testing. *J Allergy Clin Immunol* 1986;78:358-64.
18. Rafferty P, Ng WH, Phillips G, et al. The inhibitory actions of azelastine hydrochloride on the early and late bronchoconstrictor responses to inhaled allergen in atopic asthma. *J Allergy Clin Immunol* 1989;84:649-57.
19. Rafferty P, Harrison PJ, Aurich R, et al. The in vivo potency and selectivity of azelastine as an H1 histamine-receptor antagonist in human airways and skin. *J Allergy Clin Immunol* 1988;82:1113-8.
20. Welsh EJ, Bara A, Barley E, et al. Caffeine for asthma. *Cochrane Database Syst Rev* 2010;2010:CD001112.
21. Shim JS, Ahn KM, Kim MH, et al. Lower baseline FEV1 is associated with greater FEV1 improvement after tiotropium add-on in uncontrolled asthma. *Medicine* 2025;104:e44912.
22. Josephs LK, Gregg I, Mullee MA, et al. A longitudinal study of baseline FEV1 and bronchial responsiveness in patients with asthma. *Eur Respir J* 1992;5:32-9.
23. Belvisi MG, Dale N, Birrell MA, et al. Bronchodilator activity of bitter tastants in human tissue. *Nat Med* 2011;17:776-8.

24. Charous BL, Halpern EF, Steven GC. Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma. *J Allergy Clin Immunol* 1998;102:198-203.
25. Cohen AB, Girard W, Mclarty J, et al. A controlled trial of colchicine to reduce the elastase load in the lungs of ex-cigarette smokers with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;143:1038-43.
26. Conaway Jr S, Huang W, Hernandez-Lara MA, et al. Molecular mechanism of bitter taste receptor agonist-mediated relaxation of airway smooth muscle. *FASEB J* 2024;38:e23842.
27. Woo J-AA, Castaño M, Kee TR, et al. A Par3/LIM kinase/cofilin pathway mediates human airway smooth muscle relaxation by TAS2R14. *Am J Respir Cell Mol Biol* 2023;68:417.
28. Bachert C, Maspero J. Efficacy of second-generation antihistamines in patients with allergic rhinitis and comorbid asthma. *J Asthma* 2011;48:965-73.
29. McTavish D, Sorkin EM. Azelastine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs* 1989;38:778-800.
30. Simons FER. Is antihistamine (H₁-receptor antagonist) therapy useful in clinical asthma? *Clin Exp Allergy* 1999;29:98-104.
31. Katayama S, Tsunoda H, Sakuma Y, et al. Effect of azelastine on the release and action of leukotriene C₄ and D₄. *Int Arch Allergy Appl Immunol* 1987;83:284-9.
32. An SS, Wang WCH, Koziol-White CJ, et al. TAS2R activation promotes airway smooth muscle relaxation despite $\beta(2)$ -adrenergic receptor tachyphylaxis. *Am J Physiol Lung Cell Mol Physiol* 2012;303:L304-11.
33. Kamila T, Agnieszka K. An update on extra-oral bitter taste receptors. *J Transl Med* 2021;19:440.

Online supplementary material

Supplementary Figure 1. Meta-regression analysis of the mean difference in FEV1 by (A) sex, (B) median age, and (C) baseline FEV1.

Supplementary Figure 2. Leave-one-out sensitivity analysis.

Supplementary Table 1. Summary of the sensitivity analysis.

Table 1. Characteristics of the studies included in the meta-analysis.

Study	Country	Sample size	Asthma severity	Selected dose	Mode of administration	Age range	% male	Outcomes measure
Kemp <i>et al.</i> (1987)	USA	150	Moderate to severe	4 mg	Oral tablets	12-60	86%	FEV1, FVC, FEF ₂₅₋₇₅ , PEFR
Azelastine-Asthma Study Group (1996)	USA	232	Not clear	4 mg	Oral tablets	12-74	43%	FEV1, decrease in medication use, symptom score
Chervinsky <i>et al.</i> (1995)	England	120	Not clear	4 mg	Oral tablets	12-71	43%	FEV1, FVC, FEF ₂₅₋₇₅ , PEFR
Albezzaz <i>et al.</i> (1988)	Scotland	10	Mild	8.8 mg	Oral tablets	22-40	50%	FEV1
Tinkelman <i>et al.</i> (1990)	USA	99	Moderate to severe	4 mg	Oral tablets	12-61	73%	FEV1, FVC, FEF ₂₅₋₇₅ , PEFR
Ollier <i>et al.</i> (1986)	England	17	Mild	4.4 mg	Oral tablets	20-33	65%	FEV1
Rafferty <i>et al.</i> (1989)	England	11	Not clear	8.8 mg	Oral tablets	19-57	54%	FEV1
Raffarty <i>et al.</i> (1988)	England	10	Mild	17.6 mg	Oral tablets	34-53	/	FEV1

FEV1, forced expiratory volume in one second; FVC, forced vital capacity. FEF, forced expiratory flow; PEFR, peak expiratory flow rate.

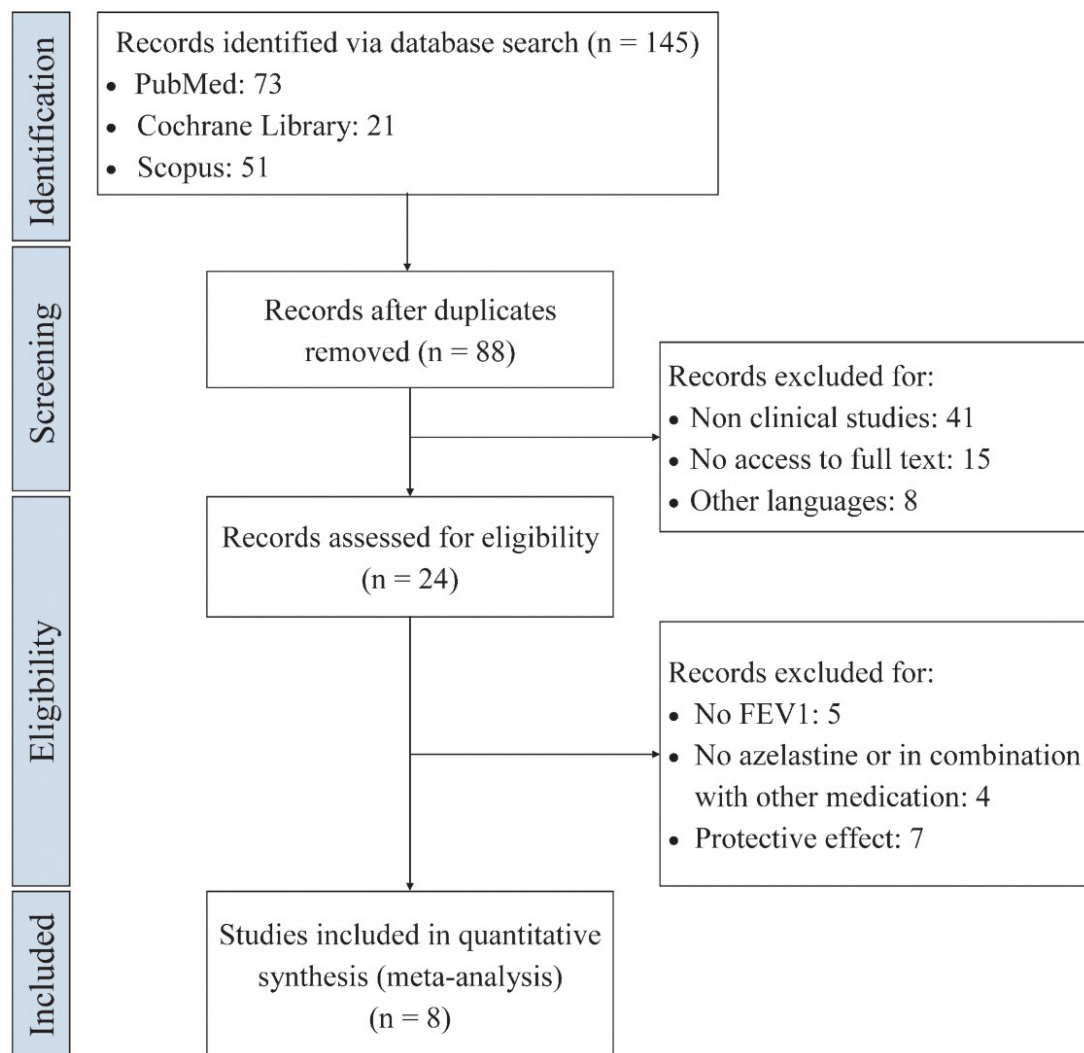


Figure 1. PRISMA flow chart of the study selection process.

Studies	Domains					Overall RoB
	D1	D2	D3	D4	D5	
Kemp et al. (1987)						
Azelastine-Asthma study group (1996)						
Chervinsky et al. (1995)						
Albezzaz et al. (1988)						
Tinkelman et al. (1990)						
Ollier et al. (1986)						
Rafferty et al. (1989)						
Rafferty et al. (1988)						

D1: Risk of bias arising from the randomization process. D2: Risk of bias due to deviations from the intended interventions. D3: Missing outcome data. D4: Risk of bias in measurement of the outcome. D5: Risk of bias in selection of the reported results.

-  Low risk of bias
-  High risk of bias

Figure 2. Quality evaluation of the selected studies.

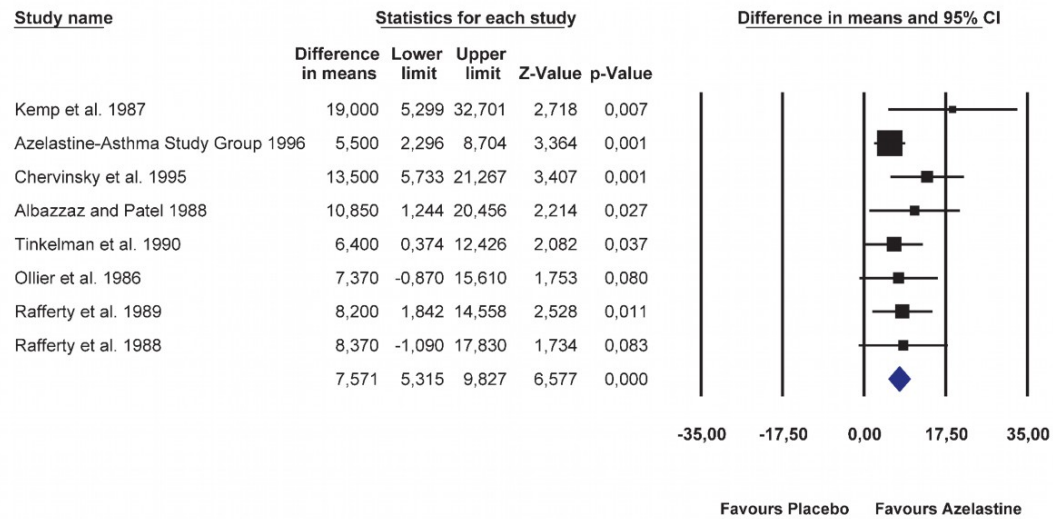


Figure 3. Forest plot of the pooled effect of azelastine on baseline FEV1.

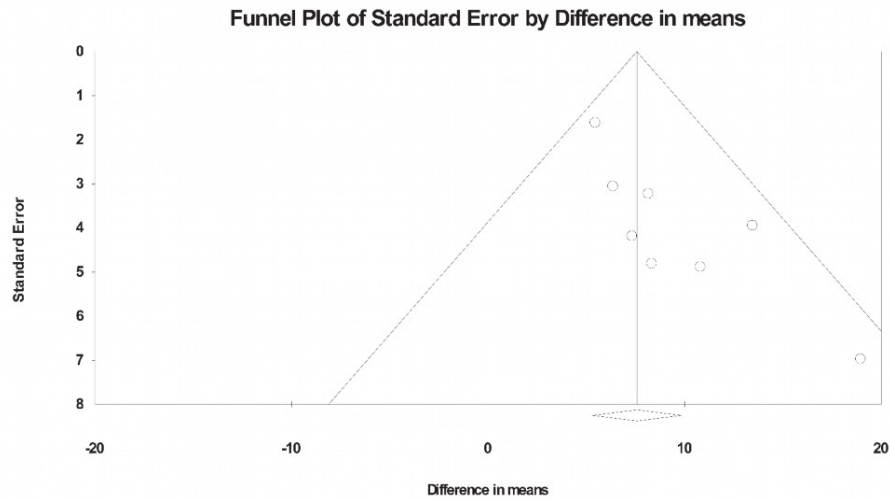


Figure 4. Funnel plot assessing the publication bias.