INPLASY

INPLASY2025120091

doi: 10.37766/inplasy2025.12.0091

Received: 27 December 2025

Published: 27 December 2025

Comparative Efficacy and Safety of Extra-fine versus Fine Particle Inhaled Corticosteroids in Asthma: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025120091

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 December 2025 and was last updated on 27 December 2025.

INTRODUCTION

Review question / Objective We will conduct a systematic review and meta-analysis to compare the efficacy and safety of extra-fine versus fine-particle inhaled corticosteroid (ICS) in adults with asthma, while controlling for inhaler type and drug properties to minimize confounding.

Rationale Evidence regarding the clinical relevance of ICS particle size in asthma remains conflicting.

Condition being studied This systematic review and meta-analysis of randomized controlled trials (RCTs) will evaluate the clinical efficacy and safety of ICS with different particle sizes in patients with asthma.

METHODS

Search strategy We will systematically search PubMed, Embase, and the Cochrane Central Register of Controlled Trials from database inception to July 31, 2025, without language restrictions, to identify relevant RCTs. Key search terms, including MeSH and Emtree, comprised "asthma," "extra-fine particle inhaled corticosteroids," and "fine particle inhaled corticosteroids." We will also manually screen the reference lists of eligible articles and relevant reviews to identify additional studies.

Participant or population Asthma patients.

Intervention Extra-fine particle size ICS (Ciclesonide, Beclomethasone dipropionate/formoterol fumarate).

Comparator Fine particle size ICS (Fluticasone propionate, Budesonide/formoterol fumarate).

Study designs to be included Randomized controlled trials.

Eligibility criteria
Inclusion criteria:
Single component: Ciclesonide vs. Fluticasone propionate
ICS/LABA combination: Beclomethasone dipropionate/formoterol fumarate vs. Budesonide/formoterol fumarate
Exclusion criteria:
Age < 12 years old
Different inhaler types
Combined with other chronic airway diseases
Ongoing trials.

Information sources We will systematically search PubMed, Embase, and the Cochrane Central Register of Controlled Trials. We will also manually screen the reference lists of eligible articles and relevant reviews to identify additional studies.

Main outcome(s)
Efficacy:
Risk of asthma exacerbation
AQLQ scores change from baseline
FEV1 change from baseline
Safety:
Risk of acute nasopharyngitis
Risk of pharyngolaryngeal pain
Risk of bronchitis
Risk of upper respiratory tract infection.

Quality assessment / Risk of bias analysis We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for assessing the certainty of evidence. Additionally, we will utilize Cochrane RoB 2.0 for the risk of bias analysis.

Strategy of data synthesis Given the anticipated clinical and methodological heterogeneity across the included RCTs, we will apply a random-effects model a priori. For dichotomous outcomes, we will calculate pooled risk ratios (RRs) with corresponding 95% confidence intervals (CIs). For continuous outcomes measured on the same scale, we will pool mean differences (MDs) with 95% CIs; when different scales were used to assess the same construct, we will instead calculate standardized mean differences (SMDs). Statistical heterogeneity will be evaluated using the I^2 statistic, with values greater than 50% regarded as indicating substantial heterogeneity. When at least 10 RCTs contributed data to a given outcome, we will plan to assess the potential for publication bias by visual inspection of funnel plot symmetry.

Subgroup analysis To explore potential sources of heterogeneity and effect modification, we will conduct prespecified subgroup analyses according to therapy type (single ICS therapy or combination), age group (trials enrolling adults only vs those including children or adolescents), ICS dose in single-therapy regimens (80 ug, 160 ug, 320 ug once daily) and baseline asthma severity (mild or moderate).

Sensitivity analysis When high heterogeneity persisted, we will further examine the robustness of the findings through sensitivity analyses, including leave-one-out influence analyses and meta-regression.

Language restriction No language restrictions.

Country(ies) involved Taiwan.

Keywords Asthma; Inhaled corticosteroid; Extra-fine particle; Fine particle; Particle size.

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