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FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Laboratório de Farmacologia Clínica e Terapêutica

Magnitude of the placebo response in both safety and efficacy in paediatric patients with severe asthma under therapy with biological agents

A systematic review and meta-analysis

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ABRIL'2023

Aknowledgments

To my supervisor, Prof. Ricardo Fernandes, for the monitoring and guidance throughout this work.

To Luísa Prada and Gonçalo Duarte for all the help and availability provided for the development of this work.

To my parents for all the support and unconditional love they give me every day.

To Leta for being a safe haven throughout this journey.

To my sisters for being my best friends and confidants.

To my grandmother for being my number 1 fan. And to my grandfather - I wish you were here for this.

To all my friends for being the best company I could have had along this journey.

Abstract

Background: Uncontrolled severe asthma is associated with increased mortality, morbidity, diminished quality of life and increased health expenditures. The development of modern biological therapy has revolutionized severe asthma treatment. Biological agents such as anti-IL5, anti IgE, anti IL4/IL13 and Anti-TSLP drugs are currently approved for the treatment of severe asthma in paediatric patients.

Objective: To assess the magnitude of the response to placebo intervention in both safety and efficacy in paediatric patients with severe asthma under therapy with approved biological agents.

Methods: We searched and screened for randomized controlled trials (RCTs) of biological agents that included a placebo comparator group and reported data from paediatric population with severe asthma published from 1968 to October 2022 in the electronic databases MEDLINE and EMBASE. The main outcomes to be evaluated in the placebo arm were: the "placebo response", defined as efficacy outcomes evaluated as change from baseline (exacerbation rate, asthma control, quality of life and lung function); and safety outcomes – ie "nocebo response", defined as the proportion of patient withdrawals, adverse events and serious adverse events. Random-effects meta-analysis was used to pool data. Statistical heterogeneity was assessed with I^2 statistic.

Results: 9 RCTs were included assigning 1031 participants with severe asthma under 18 years to the placebo arm. The proportion of asthma exacerbations (as defined by treatment with a course of systemic corticosteroids, with or without hospital attendance or admission) was 85%. The placebo response in the evaluation of the percentage of predicted prebronchodilator FEV_1 ($ppFEV_1$) was an increase mean of 2.30 percentage points (95% CI -0.10 to 4.70; P < 0.001). Pooled placebo response across all efficacy endpoints presented high heterogeneity. Pooled nocebo response reporting adverse events across the studies was 71% (95% CI 49 to 87; I^2=96%), that was greater in trials with a longer duration.

Conclusions: The high heterogeneity presented suggests not only methodological and clinical heterogeneity among the different trials, but also suggests the importance of the heterogeneity of the disease itself – severe asthma. These results are relevant for the

design and interpretation of future paediatric clinical trials, and there is significant room for improvement in the studies' design.

Resumo:

Contexto: A asma severa não controlada está associada a um aumento da mortalidade, morbilidade, diminuição da qualidade de vida e aumento das despesas em saúde. O desenvolvimento de agentes terapêuticos como os biológicos revolucionou o tratamento de asma severa. Os agentes biológicos tais como anti-IL5, anti-IgE, anti IL4/IL13 e anti-TSLP estão atualmente aprovados para o tratamento da asma severa em doentes pediátricos.

Objetivo: Avaliar a magnitude da resposta à intervenção com placebo tanto na segurança como na eficácia em doentes pediátricos com asma severa sob terapia com agentes biológicos.

Métodos: Procurámos e analisámos ensaios controlados aleatórios (RCTs) de agentes biológicos que incluíam um grupo comparador de placebo e dados relatados da população pediátrica com asma severa, publicados de 1968 a outubro de 2022 nas bases de dados eletrónicas MEDLINE e EMBASE. Os principais resultados a serem avaliados no braço placebo foram: a "resposta placebo", definida como resultados de eficácia avaliados como mudança da linha de base (taxa de exacerbação, controlo da asma, qualidade de vida e função pulmonar); e resultados de segurança - ou seja, "resposta nocebo", definida como a proporção de perda de seguimento de doentes, eventos adversos e eventos adversos severos. A meta-análise de efeitos aleatórios foi utilizada para reunir dados. A heterogeneidade estatística foi avaliada com a estatística I^2.

Resultados: 9 RCTs foram incluídos, totalizando 1031 doentes pediátricos com asma severa no braço placebo. A resposta placebo em todos os parâmetros de eficácia apresentou elevada heterogeneidade, não permitindo tirar conclusões estatisticamente significativas sobre o efeito placebo. Destacamos que a proporção de exacerbações de asma (definida pelo tratamento com um curso de corticosteroides sistémicos, com ou sem assistência ou admissão hospitalar) foi de 85% (95% CI 0 a 1,76, I2=0%) no braço placebo. A resposta placebo na avaliação da percentagem prevista de FEV1 pré-

broncodilatador (ppFEV1) foi um aumento médio de 2,30 pontos percentuais. A resposta Nocebo que relatou a proporção de eventos adversos na totalidade dos estudos foi de 71% (95% CI 49 a 87; I2=96%), sendo mais elevada nos ensaios com maior duração.

Conclusões: A elevada heterogeneidade apresentada sugere não só heterogeneidade metodológica e clínica entre os diferentes ensaios, mas também sugere a importância da heterogeneidade da própria doença - asma severa. Estes resultados são relevantes para o desenho e interpretação de futuros ensaios clínicos pediátricos, demonstrando uma margem significativa para melhorias destes ensaios.

Keywords: Severe Asthma, Paediatric, Randomized Controlled Trials, Biological Agents, Placebo Effect, Nocebo Effect, Systematic Review, Meta-Analysis

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List of Abbreviations

'Anti-IgE'- Anti immunoglobulin E

'Anti- IL5' – Anti Interleukin 5

'Anti IL4/IL13' – Anti Interleukin 4 and 13

'RCT/RCTs' – Randomized Controlled Trial/s

'mAbs' – Monoclonal Antibodies

'ICS' – Inhaled Corticosteroids

'LABA' – Long-acting Beta agonists

'LAMA' – Long-acting muscarinic antagonists

'LTRA' – Leukotriene Agent

'FEV_1' – Forced Expiratory Volume in the first second

'QoL' – Quality of Life

'RoB' – Risk of Bias

'ES' – Effect Size

'SD' – Standard Deviation

'CASI' – Composite Asthma Severity Index

'ACQ' – Asthma Control Questionnaire

'AQLQ' – Asthma Quality of Life Questionnaire

'CI' – Confidence Interval

'SAEs' – Serious Adverse Events

'AE' – Adverse Event

'PAQLQ' – Paediatric Asthma Quality of Life Questionnaire

'ppFEV$_1$' – percentage predicted Forced Expiratory Volume in the first second

'GINA' – Global Initiative for Asthma

'ERS/ATS' – European Respiratory Society and American Thoracic Society

'EPR-3' – Expert Panel Report 3

'SMART' – Single maintenance and reliever therapy

Introduction

Asthma is a chronic inflammatory disease of the respiratory system characterized by bronchial hyperresponsiveness, episodic acute asthma exacerbations, and reversible airflow obstruction (Reddel et al., 2022). This is a prevalent disease among the paediatric population, affecting about 14% of children globally, with a rising prevalence worldwide (Zar & Ferkol, 2014) . Although most children achieve disease control with low-dose inhaled corticosteroids, there are approximately 5 to 10% of children with severe asthma, which results in substantial health care costs, caregiver burden, impaired quality of life and increased risk for abnormal lung growth (Chung et al., 2014; Ramratnam et al., 2017). In recent years a growing number of targeted biological agents (including anti- IgE; anti- IL5; Anti IL4/IL13; Anti-TSLP) have been approved and recommended as step 5 add on therapy, according to GINA guidelines for children with severe asthma (Reddel et al., 2022).

The standard to evaluate new pharmacological interventions, including biological agents, are randomized clinical trials (RCT) with placebo as a control arm. The placebo response is defined as the result produced by administering an inactive treatment such as placebo in all health outcomes, which may be due to regression to the mean and natural course of disease (Evers et al., 2018). Though lacking pharmacologic activity, placebos have been shown to potentially have an effect and improve signs and symptoms for a wide variety of human diseases, such as depression, both in research trials and in actual clinical practice (Fountoulakis et al., 2015).This phenomenon is a challenge for researchers; however, attention has begun to focus on trying to understand and quantify the magnitude of the placebo response.

The placebo response can be problematic when designing and analysing clinical trials since phenomena such as a strong placebo effect that decreases the difference between an active intervention compared with placebo, or a strong nocebo effect that may mask potentially important safety signs, (Chavarria et al., 2017) may be confounding factors in the assessment of both efficacy and safety of a drug in a clinical trial (Enck et al., 2008). Asthma can be a good disease model to study placebo effects since it can be evaluated through objective end-points and medical intervention can rapidly change baseline lung

function or airway inflammation, even if the disease symptoms are subjective by nature (Busse & Lemanske, 2009; Dutile et al., 2014).

Monoclonal antibodies (mAbs, 'Biologics') are proteins designed to homogeneously bind to a specific antigen. The resultant immune response ranges from ligand inactivation to cytotoxicity and is determined by the mAb isotype and structure. As with many other inflammatory diseases, the therapeutic landscape of asthma has been transformed since the approval of a first therapeutic mAb- omalizumab (Dragonieri & Carpagnano, 2021). They constitute an add-on therapeutic tool when treatment control is inadequate and/or exacerbations are frequent under inhaled treatment. The application of currently approved add-on treatments for severe asthma in children, such as omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab have been shown to be effective in terms of asthma control and exacerbation rate. (Perikleous et al., 2022).

However, data available specifically for the paediatric population is often limited, as there is a clear mismatch between paediatric RCT activity and paediatric disease burden (Bourgeois, 2013). This results in a need to generalize or extrapolate research findings from adults to children and adolescents, not allowing children to fully share the benefits derived from advances in medical science (Institute of Medicine (US) Committee on Clinical Research Involving Children, 2004). Thus, the selection of the appropriate biologic agent, the potential predictors of good asthma response, and the long-term outcome in the paediatric population has a limited evidence base.

Consequently, we undertook a systematic review of the placebo response in biological therapy in clinical trials of severe asthmatic children and adolescents to characterize its magnitude and identify its determinants. Our main aim was to evaluate the impact and importance of the placebo response and understand how to use this knowledge to inform decisions in future clinical trial design.

Formatou: Inglês (Reino Unido)

Methods

This systematic review followed the reporting principles of the Preferred Reporting Items for Systematic Reviews and Meta-analyses.(Moher et al., 2009)

Data sources and search strategy

We searched for the published studies through a computerized search on the following electronic databases: PubMed and EMBASE. Clinical trial registries (WHO International Clinical Trials Registry Platform and Clinicaltrials.gov) were also searched. Reference lists of included studies were crosschecked for additional citations. Studies published from 1968 to October 2022 were included in this article. Both details from search strategies for Medline, Embase and registers can be found in the **Appendix**.

Study selection

Only randomized clinical trials with one or more experimental treatment intervention group and a placebo comparator group were considered eligible.

Types of studies

We included randomised controlled trials (RCTs), studies reported in full text, those published as an abstract only, and unpublished data. Non-randomised studies were excluded.

Types of participants

We included data from studies that included and reported data on paediatric subjects (younger than 18), with a diagnosis of severe asthma defined, pragmatically, as people enrolled in RCTs studying this condition.

Trials enrolling primarily adults but including participants under age 18 years are also accepted, providing that they fulfilled the diagnostic criteria and that the outcomes for this age group were reported separately.

Types of interventions

Studies that compare the following were included:

1. Anti-interleukin-13 or -4 agents with placebo (Some agents may inhibit both interleukin-13 and -4).
2. Anti-Immunoglobulin E (IgE) agents with placebo.
3. Anti-interleukin-5 agents with placebo.
4. Anti-TSLP with placebo

Studies that included following co-interventions, provided they are not a stand-alone randomised treatment arm: individuals' usual short- or long-acting medications (e.g. inhaled corticosteroids, long-acting beta adrenoceptor agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists) or other pharmacological interventions used in severe asthma, were included.

Types of outcome measures

Main Outcomes

The primary efficacy outcome will be: “Placebo response”, defined as efficacy outcomes evaluated as change from baseline in the placebo arm. Specifically, the following outcomes were analysed: Change from baseline in quality of life assessments and change from baseline in asthma control (which can be assessed by any scale for evaluation of quality of life in asthma patients); Change from baseline in asthma exacerbations (defined pragmatically according to the RCT), and change from baseline in lung function (FEV1 evaluation). These efficacy outcomes were chosen as they are core outcome measure sets for paediatric and adults with severe asthma (Khaleva et al., 2022).

The primary safety outcome was: “Nocebo response”, evaluating the proportion of patients experiencing adverse events, serious adverse events, and withdrawals in the placebo arm.

Reporting one or more of the outcomes listed here in the study is not an inclusion criteria for the review.

Screening

Two independent reviewers (IF and LP) screened the references identified by the search strategy, accessing both the titles and abstracts, and excluding references not applicable according to the eligibility criteria. If any disagreement existed, they were solved through discussion or, when necessary, by a third author. Two independent reviewers (IF and LP) screened the full-text articles to include the studies that fulfilled the inclusion criteria. When disagreements arose, they were resolved through discussion or, if necessary, through the consultation of a third author.

Data extraction and risk of bias assessment

Two reviewers (IF and GD) independently extracted the characteristics and data (methodological characteristics, patients' characteristics, outcome assessment, inclusion and exclusion criteria, placebo, and active arm characteristics) from the eligible studies. We extracted data for each outcome at the time point closest to the end of the treatment period. Where multiple outcomes are proposed (i.e. as for lung function), data for all available measures was extracted. These data sets were checked against each other, and any disagreements were resolved by arbitration and consensus or by consultation with a third reviewer.

Risk of bias of included studies was evaluated with the use of the Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) tool (*Risk of Bias 2 (RoB 2) Tool | Cochrane Methods*, n.d.). This tool was constructed to incorporate several sources of bias such as randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Effectively, we rated as low, unclear, or high risk of bias according to the previous items. As for general risk of bias, a moderate risk study would not have all items classified as low risk, and a high risk study would have any item deemed as high risk. One author assessed risk of bias domain and any issues that arose were solved by discussion with a second author.

Statistical Analysis and Pooled Data Evaluation

Only the data regarding the placebo arm was collected and analysed. The placebo and nocebo data were retrieved from the last time point proposed in the placebo arms of RCTs. For continuous outcomes we used effect size (ES) as an outcome effect measure. The ES was calculated as the quotient of the mean change from baseline divided by the SD at baseline, correcting for small-sample bias (Hedges & Olkin, 2014). We entered data presented on a scale with a consistent direction of effect. Positive changes indicate improvement in quality of life (AQLQ) and FEV1, whereas negative changes indicate improvement in asthma control (CASI; ACQ). We synthesised data relating to exacerbations based on the number of exacerbations per patient during the treatment period (an annualized asthma exacerbation rate), using rates.

All data were pooled using a random effects model.

In some trials, SD was obtained from standard error or confidence intervals (CI). We also performed the analyses with the mean change from baseline and SD, using the natural units of the most applied scale for each outcome. When a different scale was used, linear rescaling to the chosen instrument was conducted (Thorlund et al., 2011). Dichotomous outcomes are reported as proportions. Heterogeneity between trial results was tested using I^2. (Higgins et al., 2003; Higgins & Thompson, 2002) An I^2 value of 30% to 60% may represent moderate heterogeneity, a value of 50% to 90% may represent substantial heterogeneity and a value of 75% to 100% may represent considerable heterogeneity(Deeks, 2022). If we identified substantial heterogeneity, we reported it and explored the possible causes. All results are presented with a 95% CI.

Results

Search Results

The search strategy retrieved 1008 records. After duplicates were excluded, 922 records were identified. A total of 277 records were appraised in full. From this full text analysis records were excluded due to population not relevant (did not include paediatric population or there was no separation of results for patients under 18 years old), study designs and publication type (not Randomized Clinical Trials), outcome, absence of a placebo arm as control arm. A total of 9 studies met the inclusion criteria.

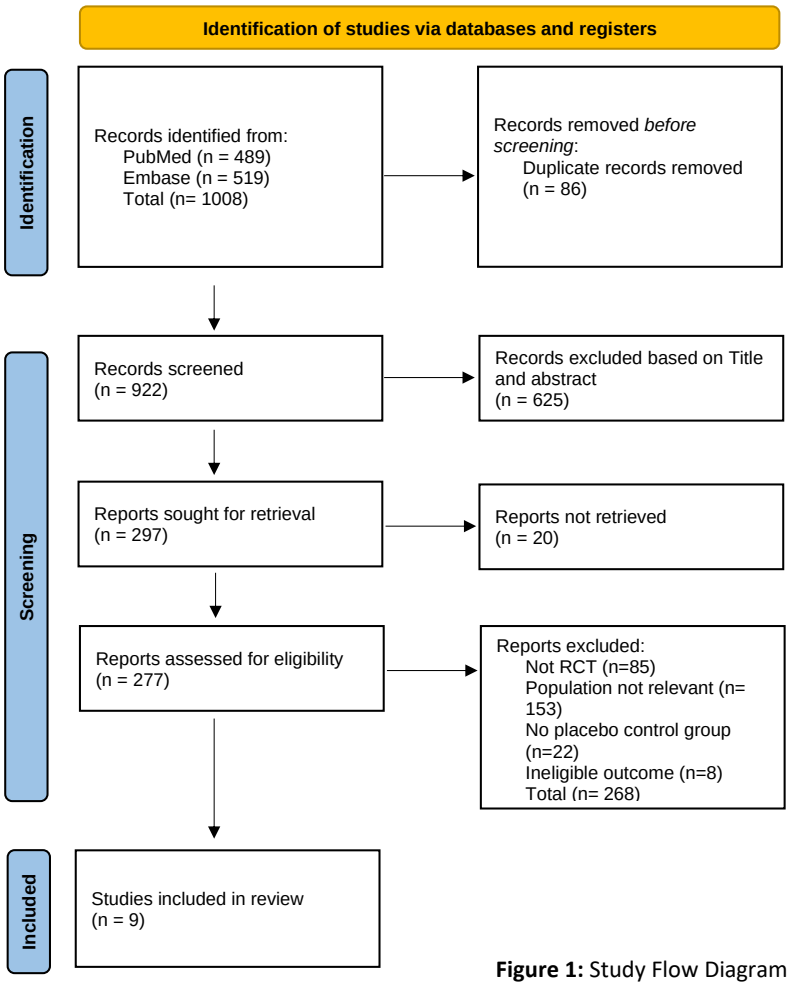

Figure 1: Study Flow Diagram

Characteristics of included studies

The main characteristics of the 9 studies (Bacharier et al., 2021; Berger et al., 2003; Busse et al., 2011; Jackson D.J. et al., 2022, p. 202; Kulus et al., 2010; Menzies-Gow A. et al., 2020; Milgrom et al., 2001; Szefler et al., 2022; Teach et al., 2015) are included in Table 1 and 2 in the Appendix. Overall, all studies recruited children or adolescents with ages for participants ranging between 6 and 17 years old. A total of 1031 paediatric participants. All studies were conducted between 2001 and 2022, most were international and multicentre clinical trials, with only 3 being single-nation and one single-centre. All studies were parallel trials, most of them being on phase 3 of clinical trial (with only 2 being on phase 4 and one on phase 2). All studies presented at least two study arms (active + control), with dosing of the active and the placebo treatment according to either the participants' weight or age. One study, Teach 2015, presented 3 study arms (omalizumab (with inhaled placebo), ICS boost (with injected placebo), or guidelines-based care with injected placebo and inhaled placebo). The percentage of female in the studies ranged between 60% and 30%. Studies had a duration of between 90 days and 60 weeks.

The percentage of patients diagnosed in the placebo arm receiving a baseline therapy of corticosteroid and LABA (long acting beta adrenergic) twice daily with or without a Leukotriene antagonist (such as Montelukast) ranged from 21% to 64,9%. Baseline predicted FEV1 in the placebo arm ranged between 70% and 93%.

Therapeutic interventions were the following biological agents: Mepolizumab, Tezepelumab, Lebrikuzumab, Dupilumab and Omalizumab, administered via injection. Placebo was also administered via injection in all trials.

The primary endpoint of the included RCTs was the evaluation of asthma exacerbation (defined by treatment with a course of systemic corticosteroids, with or without hospital attendance or admission) measured either through a proportion (number of participants experiencing at least one asthma exacerbation during the trial), which was the case of *Teach 2015, Milgrom 2001 and Busse 2011*, or through an annualized rate of severe asthma exacerbations, *Jackson 2022, Bacharier 2021, Menzies-Gow 2020* and *Kulus*

2010. Two studies, Berger 2003 and Milgrom 2001, had as their primary endpoint evaluating the safety, tolerability and corticoid sparing effect of the biological agent.

Three trials evaluated change from baseline in quality of life, using both ACQLQ+12 (*Szefler 2022*) and PAQLQ (*Bacharier 2021* and *Kulus 2010*) scales.

Four trials *(Jackson 2022, Bacharier 2021, Teach 2015* and *Busse 2011*) reported paediatric results for the assessment of FEV_1 change from baseline, reporting an evaluation of the percentage of predicted prebronchodilator FEV_1.

To assess Asthma Control three different scales were used: CASI (by *Jackson 2022*); ACQ-5 (by *Szefler 2022*) and ACQ-7 IA (by *Bacharier 2021*)

Risk of Bias

Figure 2 provides a summary of risk of bias judgements, presented by study and domain (randomisation process; deviations from the intended interventions; missing outcome data; measurement of the outcome and selection of the reported result). **Figure 3** depicts the risk of bias for each domain, presented as percentages across all included studies.

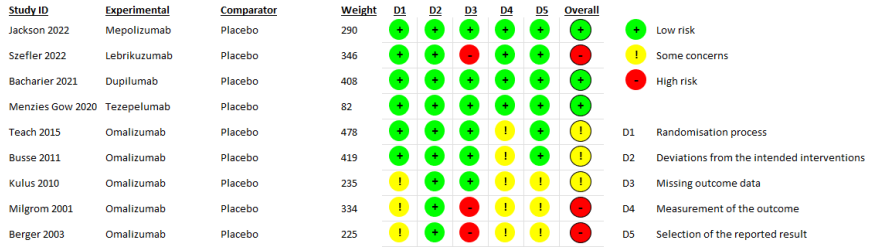

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

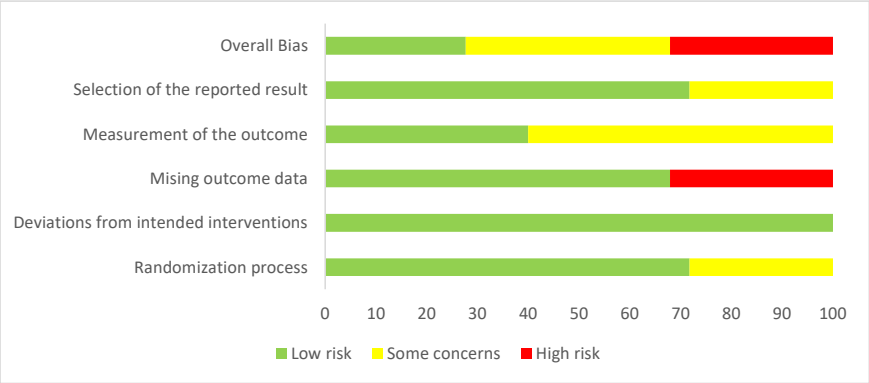

Figure 3: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Randomization Process: Six studies employed adequate methods of random sequence generation and were considered to be at low risk of bias (Jackson 2022; Szefler 2022; Bacharier 2021; Menzies-Gow 2020; Teach 2015 and Busse 2011).Three studies provided insufficient information regarding methods of random sequence generation (Kulus 2010; Milgrom 2001 and Berger 2003) and two studies provided insufficient information regarding concealment of treatment allocation (Milgrom 2001 and Berger 2003) to allow a judgement on risk of bias; the risk of bias for these studies was rated as unclear/some concerns.

Deviations from intended interventions: Concerning the blinding of participants, carers and people delivering the interventions, all studies were considered at a low risk of bias. As a result, since there was a correct blinding through all studies both objective and subjective outcomes were considered to be at low risk of bias.

Missing Outcome Data: We considered 6 of 9 studies (Jackson 2022; Bacharier 2021; Menzies-Gow 2020; Teach 2015; Busse 2011 and Kulus 2010) to be at low risk of attrition bias on the basis of low and balanced rates of participant withdrawal, which were adequately documented in the trial reports. Three studies (Szefler 2022, Berger 2003 and Milgrom 2001) were considered to be at high risk for attrition bias based on either a high proportion of withdrawals in one or more treatment arms (in Szefler 2022,

withdrawal rates were 44%), an uneven proportion of withdrawals between treatment arms, or both, and not enough information regarding these parameters.

Measurement of the Outcome: Four studies (Jackson 2022; Szefler 2022; Bacharier 2021 and Menzies-Gow 2020) were classified as low risk of bias, since outcome assessors were blinded for the intervention received by study participants, measurement or ascertainment of the outcome did not differ between intervention groups, and the methods used for measuring outcomes were appropriate. Five studies (Teach 2015; Busse 2011; Kulus 2010; Berger 2003; Milgrom 2001) were considered unclear/some concerns regarding risk of bias since no information was available regarding blinding of outcome assessors, or blinding of outcome assessors was not ensured.

Selection of the reported result: Six studies were considered at low risk of bias (Jackson 2022; Szefler 2022; Bacharier 2021; Menzies-Gow 2020; Teach 2015 and Busse 2011). Three studies (Kulus 2010; Milgrom 2001 and Berger 2003) were rated as unclear/some concerns due to lack of information (no pre-specified analysis plan was available, there were multiple possible outcome measurements within the outcome domain, especially regarding different time points for FEV1 evaluation).

Synthesis of Results

Efficacy outcomes:

Asthma exacerbations

Four studies reported an annualized rate of severe asthma exacerbations, among these studies the pooled placebo response was a rate of 0.85 (95% CI 0 to 2.90; 4 studies, n= 512), with a low statistical heterogeneity (I^2=0%) and a p value of 0.97.

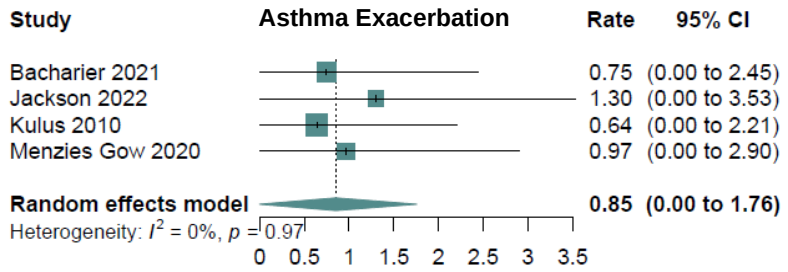

Figure 4: Forest-plot for asthma exacerbation rate in the placebo arm

Four studies reported the incidence of asthma exacerbation in its total population. From these, two studies evaluated the incidence of exacerbations in a period from 3 to 4 months; proportion of exacerbations in the placebo arm was 26% (95% CI 0.20 to 0.32), with a low statistical heterogeneity (I^2=0%) and a p value of 0.53.

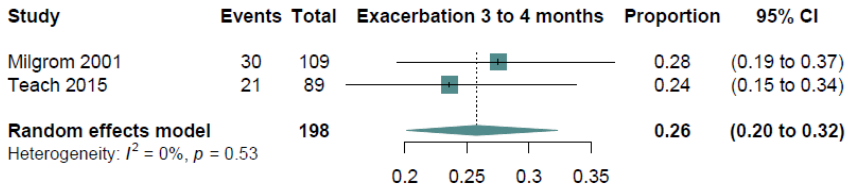

Figure 5: Forest-plot for the proportion of participants who experienced one or more severe asthma exacerbations in 3 to 4 months in the placebo arm.

The other two studies analysed the incidence of asthma exacerbations in a period from 6 to 12 months, and the proportion of exacerbations in the placebo analyses was of 47% (95% CI 0.42 to 0.53), with a low statistical heterogeneity (I^2=0%) and a p value of 0.51.

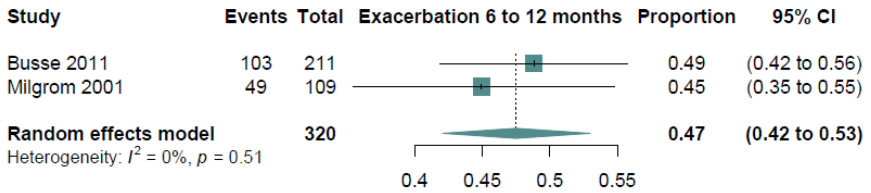

Figure 6: Forest-plot for the proportion of participants who experienced one or more severe asthma exacerbations during a period of 6 to 12 months in the placebo arm.

Change from baseline in lung function (FEV_1 evaluation)

Four studies reported an evaluation of the percentage of predicted prebronchodilator FEV_1 ($ppFEV_1$). The pooled placebo response was an increase mean of 2.30 percentage points (95% CI -0.10 to 4.70; P < 0.001), with a high statistical heterogeneity (I^2=100%).

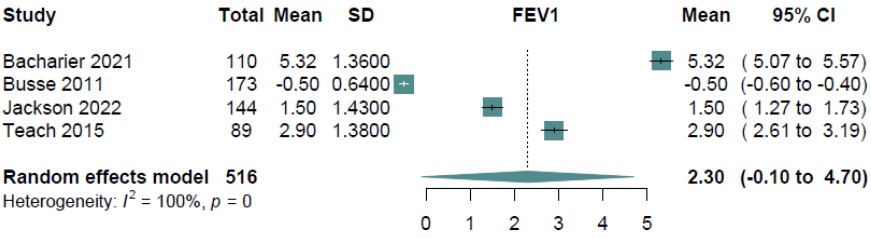

Figure 7: Forest-plot for change from baseline in the percentage of the predicted prebronchodilator forced expiratory volume in 1 second ($ppFEV_1$) in the placebo arm.

Quality of Life Assessment

Three studies reported an evaluation of quality of life (QoL) through two different disease-specific, interviewer-administered QoL questionnaire designed to measure functional impairments that are most important to children >=7 years with asthma (PAQLQ) or for children with 12 years and older (AQLQ+12). The pooled placebo response was an increase of 1.06 standardized scale units (95% CI 0.90 to 1.23; p < 0.01), with a high statistical heterogeneity (I^2=98%).

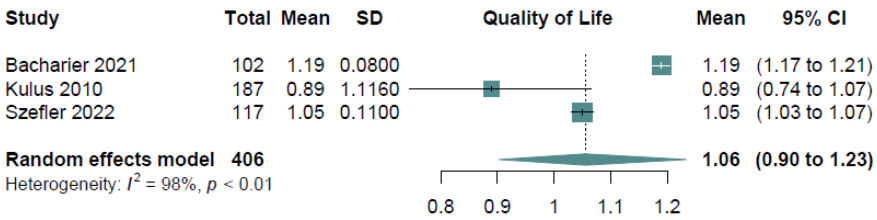

Figure 8: Forest-plot for the mean change from baseline in quality-of-life improvement in the placebo arm

Asthma Control

Three studies evaluated asthma control through different scales. Bacharier 2021 and Szefler 2022 used ACQ-7-IA (Asthma Control Questionnaire 7 Interviewer-Administered) and ACQ-5 (Asthma Control Questionnaire 5) respectively, and Jackson 2022 used CASI (Composite Asthma Severity Index), in all these scales a lower score indicated higher asthma control. As a result, the pooled placebo analyses reported a decrease of -1.34 standardized scale units (95% CI -1.99 to -0.70), with a high statistical heterogeneity (I^2=100%).

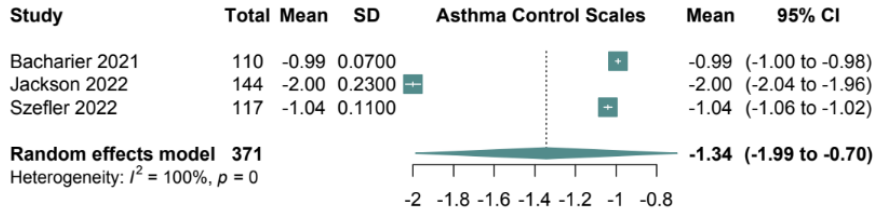

Figure 9: Forest-plot for the mean change in asthma control scales in the placebo arm

Safety Outcomes

Overall, 71% (95% CI 49 to 87; I^2=96%) of patients experienced adverse events in the placebo arm, among 8 studies (n=993).

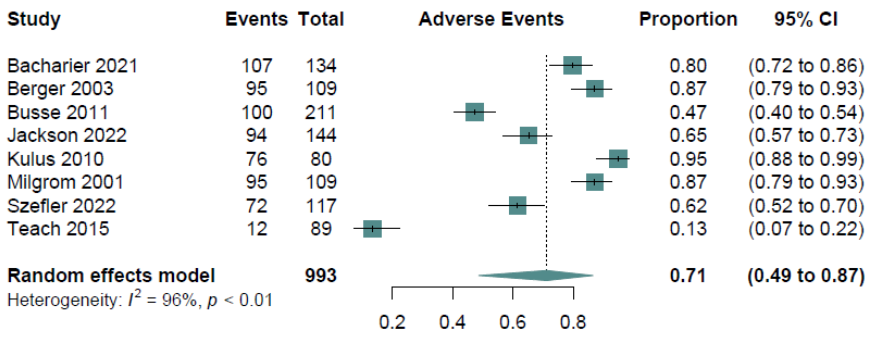

Figure 10: Forest-plot for the proportion of adverse events in the placebo arm

Regarding serious adverse events (SAEs), 5% (95% CI 2 to 9; I^2=83%) of patients experienced such events, among 7 studies (n=884).

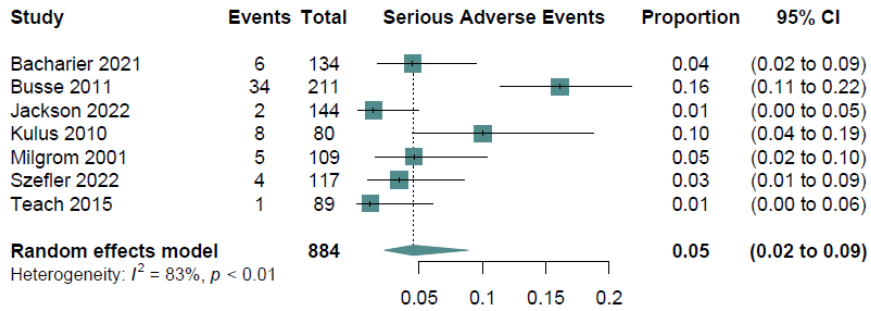

Figure 11: Forest-plot for the proportion of serious adverse events in the placebo arm

Regarding withdrawals, we estimated a proportion of 14% (95% CI 7 to 26; I^2=92%), among 7 studies (n=1012).

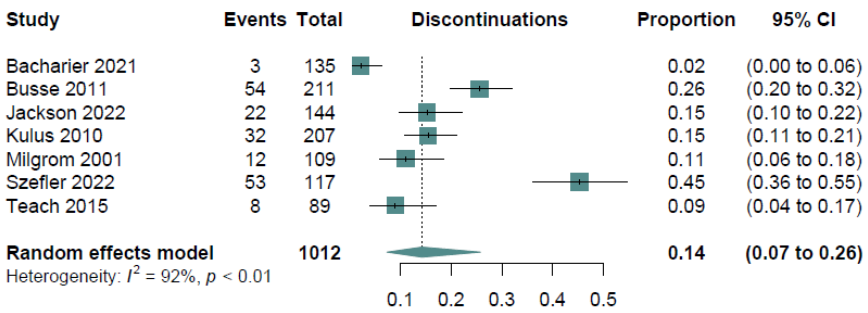

Figure 11: Forest-plot for the proportion of discontinuations in the placebo arm

Discussion

This systematic review included 9 RCTs with a total of 1031 participants in the placebo arm and demonstrated that the mean placebo response in clinical trials of Severe Asthma patients corresponds to an annualized rate of 85% in asthma exacerbations. We also documented a high rate of adverse effects 71% – the nocebo response - among placebo-treated patients and a high discontinuation proportion of 14%.

However, one may note that among all results one thing stands out: the high heterogeneity between results and consequently between different trials. Even in objective outcomes, such as FEV1, which is universally standardized (measured through spirometry and using a universal scale) and independent from patient analysis, where low heterogeneity and small to non-existent placebo response were expected (Silva et al., 2017), the percentage of predicted prebronchodilator FEV_1 varies between an increase in 5.30 percentage points and a decrease of 0.5 percentage points. It is important to stand out that although FEV_1 measurement is an objective outcome it depends on the collaboration of the participant, especially in paediatric population, which can lead to error in its measurement.

An important question emerges: where does so much heterogeneity come from? Are we dealing with great clinical heterogeneity or is the methodology between trials so different that could explain this?

Firstly, analysing clinical heterogeneity, through scanning of inclusion criteria and characteristics of the baseline population in the 9 RCTs included in this review. One possible source of heterogeneity comes from the difference between mean age of participants among trials. In fact, both *Szefler 2022* and *Menzies-Gow 2020* included only adolescent participants (with ages ranging from 12 to 17 years old), whereas in the rest of the trials participants mean age ranged between 9 and 10 years.

Main differences were found between baseline predicted FEV_1 values, since in *Szefler 2022*, *Bacharier 2021* and *Menzies-Gow 2020* FEV_1 values were respectively 70%, 78% and 62,7% at baseline in comparison with studies such as *Jackson 2022* and *Busse 2011* in which baseline population presented FEV_1 values of 92%. This can be a contributor to the heterogeneity observed in FEV_1 measures, as there were populations that were

already better optimized at the beginning of treatment and could also suffer a decrease in FEV_1 given the natural history of the disease (increase in inflammation and consequently a lower FEV_1 response), as seen in *Busse 2011*, or a lower/insignificant FEV_1 increase, *Jackson 2022* and *Teach 2015*. In contrast, patients of the *Bacharier 2021* trial presented at baseline lower FEV_1, meaning a greater potential for the patients' asthma optimization, and its greater increase in the placebo arm could be explained by the provision of a structured clinical regimen dictated by the participation in a clinical trial, where patients are more motivated and have better adherence to baseline asthma control therapy, (Luc et al., 2019).

Another clinical factor that could have contributed to the high heterogeneity found lies in the frequency of exacerbations in the baseline populations. *Jackson 2022* and *Menzies-Gow 2020* presented a more exacerbator population, with the inclusion criterion being patients with more than two asthma exacerbations in the previous year before the start of the trial, and 43% having three or more exacerbations in previous year. Whereas other trials only required at least one asthma exacerbation within one year prior to the trial, *Bacharier 2021, Szefler 2022,* which translates into a less exacerbator population with 47% of patients having at least one asthma exacerbation in previous year, *Bacharier 2021*. This could, in part, explain the heterogeneity observed in asthma control, where patients in *Jackson 2022* presented a greater asthma control at the end of the trial. These patients, as stated previously, experienced more exacerbations, and thus might have noticed and reported a greater positive difference in asthma control, when under a more controlled and rigid environment with better therapy adherence and better-than-usual clinical monitoring and patient care experienced during a clinical trial. (Luc et al., 2019)

As for methodological characteristics that could contribute to the high heterogeneity in the presented results, the following emerge: different scales to measure quality of life and asthma control improvement, different guidelines for asthma characterization and baseline and during trial therapy definition, and different baseline therapy are used between trials. Addressing the difference in scales used to measure quality of life (a subjective outcome), there were two in usage, PAQLQ (in *Bacharier 2021* and *Kulus 2010*) and AQLQ +12. These are disease-specific, interviewer-administered QoL

questionnaire designed to measure functional impairments. The AQLQ was developed for adults whereas PAQLQ was developed to measure the problems that children 7-17 years old experience. AQLQ+12 was a modification of AQLQ to make it suitable for both adolescents and adults, thus being valid in trials where patients range from 12 to 70 years. However the AQLQ +12 is not ideal for adolescents because it does not include all their problems (e.g. not being able to keep up with their friends) and should not be used in studies that only include adolescents, such as *Sfezler 2022,* instead PAQLQ should be used. (Juniper et al., 2005). In asthma control assessment we also compared results acquired from different measuring tools, such as CASI, ACQ- 5 and ACQ 7 IA. Composite Asthma Severity Index (CASI) scores included 5 domains: day symptoms and albuterol use, night symptoms and albuterol use, controller treatment, lung function measures, and exacerbations. The minimum composite score was 0 while the maximum was 20. The higher the score the more allergy symptoms a subject has (Wildfire et al., 2012). The ACQ, Asthma Control Questionnaire, was developed using expert opinion and originally contained seven items (ACQ 7 IA); however, a five-item version (ACQ-5) has been validated (O'Byrne et al., 2010). ACQ 7 IA had 7 questions, which assessed: frequency of nocturnal awakenings, severity of asthma symptoms in the mornings, limitation of daily activities, shortness of breath due to asthma and wheeze, reliever medication use, and FEV1 (% predicted), with a higher score indicating lower asthma control, whereas ACQ 5 lack the two last parameters. The results present a similar response in the placebo arm regarding improvement in asthma control in *Bacharier 2021* and *Szefler 2022* which made use of similar evaluation tools (ACQ), whereas *Jackson 2022* presented a higher increase in asthma control but also used a different questionnaire to assess (CASI).

The definition of asthma exacerbation is in itself a source of heterogeneity. Although most trials in this review adopt the following definition for asthma exacerbation: a worsening of asthma control requiring systemic corticosteroids or hospitalization (Fuhlbrigge et al., 2012), it is clear that both the perception of symptoms considered to be a worsening of asthma or the decision to institute systemic corticosteroids or hospitalize a patient are all subjective, and therefore heterogenous among participants and health practitioners.

Apart from usage of different evaluation tools for the same outcomes, not all trial protocols followed the same asthma guidelines and were carried out in different years, which can correlate to advances in medical care and asthma characterization that leads to evolution in guidelines and as such different recommendations and standard care. In fact, there is a major shift in asthma management and care with the introduction of the SMART strategy (Nalin et al., 2019), which was only followed in the most recent clinical trials (Szefler 2022 and Jackson 2022). Guidelines used were the following: GINA 2020 (Ish et al., 2021) in *Szefler 2022* and *Bacharier 2021*, ERS/ATS 2020 (Holguin et al., 2020) in *Jackson 2022*, EPR-3 (Asthma, 2007) in *Teach 2015*, *Busse 2011* and *Kulus 2010.* In both Milgrom 2001 and Berger 2003, all participants, regardless of asthma severity, underwent identical therapy - beclomethasone dipropionate 168-420 ug/day. Given the fact that different guidelines correlate to different therapeutical strategies, participants in the placebo arm were in fact under different doses of inhaled corticosteroids (ICS) or had or not a second controller medication (e.g., long-acting *β*-agonists [LABAs], leukotriene receptor antagonists [LTRAs], long-acting muscarinic antagonists [LAMAs]), as a consequence a great heterogeneity can be found in the placebo arm, due to the fact that baseline therapy would differ among trials and among participants.

Although this systematic review evaluated the magnitude of placebo response, it is important to underline what was previously stated: patients in the placebo arm despite not receiving monoclonal antibody therapy were in fact under therapy with high dose inhaled corticosteroids (ICS) and a second controller. Even with guideline-based asthma therapy, under 50% of patients have well-controlled asthma (National Asthma Education and Prevention Program, 2007). This can be related to the fact that the variable response to standardised therapy may be due to the heterogeneity of asthma, (Fajt & Wenzel, 2014; Moore et al., 2007; Wenzel, 2012, 2013), and as such be a contributing factor to the high heterogeneity found in the present review. In fact severe asthma itself is a heterogenous disease as it includes both difficult- to-control asthma (owing to inadequate or inappropriate treatment, comorbidities such as obesity, gastroesophageal reflux disease, chronic rhinosinusitis, poor adherence, and allergen exposure,…) (Yılmaz, 2018), and treatment-resistant asthma (asthma that remains

uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors)(Chung et al., 2014).

Apart from the heterogeneity observed in efficacy outcomes, the same was observed in the pooled analyses of the safety outcomes. As showed in the results concerning the incidence of adverse events, one outlier stands out, *Teach 2015*, with a lower incidence of adverse events (13%), coincidentally it is the trial with the shorter follow-up period (90 days), and as so a shorter disease progression and lower perceived dose of exposure (Webster et al., 2016). Also, there is in fact a high proportion of adverse events- 71% of participants experienced at least one adverse event during trial. In fact, asthma is a disease with a relatively high baseline symptoms and where patients but especially caregivers (such as parents) have a high self-awareness, which may serve as risk factors for greater nocebo response (Webster et al., 2016). Regarding serious adverse events, an outlier stands out, *Busse 2011*, with a proportion of 16%, this was also the trial with the longer follow-up period, i.e. 60 weeks, which can be a contributing factor for a higher number of serious adverse events (Webster et al., 2016). As for discontinuations, there is one clear outlier, Szefler 2022, which can be explained by the fact that there was a premature closing of enrolment and study drug dosing according to decision by the sponsor (Szefler et al., 2022). However, apart from the outlier, there is still significant heterogeneity and a significant proportion of discontinuations.

There are some limitations in the work presented. First the small number of participants and RCTs included in the systematic review, even though there is a significant lack of clinical trials performed in children and adolescents, and most of trials that include participants with ages between 12 to 70 years fail to report results regarding the adolescent subgroup (12-18 years), weakens our statistical power and may also contribute to the high heterogeneity observed. Furthermore, the baseline therapy used in the placebo arm differs among the different clinical trials, which constitutes a high source of heterogeneity. Since most trials fail to report a baseline annualized rate of severe asthma exacerbations, it is difficult to withdraw conclusions of significant importance regarding the possible placebo effect in decrease or increase in asthma exacerbations at the end of the trial.

Although the magnitude of our findings is not big enough to have a serious impact in the clinical scenario, it should however be of great interest for the future planning of clinical trials in paediatric severe asthma. One consideration is the importance of reporting a baseline annualized rate of severe asthma exacerbations in clinical trials, so a stronger conclusion over the magnitude of placebo effect and even drug effect can be drawn. The heterogeneity found in this systematic review can also serve as an example for the future possible use of a consensual set of guidelines equal between asthma trials, in order to have patients in placebo arm under the same baseline therapy. Moreover, this review illustrates the heterogeneity of the disease itself – asthma - in paediatric population, which underlines the importance of personalised care in the paediatric population with a severe phenotype of the disease, namely through biological agents, for a greater control and reduced disease burden. With this work it should also be reiterated the importance of conducting paediatric trials, or even more importantly of conducting a separate analysis of the results acquired in the paediatric subgroup in trials that enrol participants of multiple age groups.

To our knowledge, our work is the first systematic review done in order to evaluate both the placebo and the nocebo responses in severe asthma in paediatric population that integrate biological agents' trials, and we believe that the conclusions that we have drawn should be of paramount importance when designing and interpreting results from clinical trials in this disease.

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Appendix

Search Strategy for Embase

Database: Embase <1974 to 2022 October 28>

Date for search: 31.10.2022

Search Strategy:

1 ((child.mp. or *child/ or *pediatric patient/ or pediatric*.mp.) and *asthma/) or asthma*.mp. (326849)

2 biological factors.mp. or biological factor/ or biological agents.mp. or biological product/ or monoclonal antibodies.mp. or monoclonal antibody/ or anti-IgE antibodies.mp. or omalizumab.mp. or omalizumab/ or rhuMAb-E25.mp. or omalizumab/ or xolair.mp. or omalizumab/ or mepolizumab.mp. or mepolizumab/ or benralizumab.mp. or benralizumab/ or reslizumab.mp. or reslizumab/ or interleukin-13.mp. or interleukin 13/ or dupilumab.mp. or dupilumab/ or tezepelumab.mp. or tezepelumab/ (387660)

3 placebo effect/ or placebo/ or placebo*.mp. or salicylhydroxamic acid/ or salicylhydroxamic.mp. or sham.mp. or sham procedure/ or (dummy or dummies).mp. or fake.mp. (644837)

4 1 and 2 and 3 (2625)

5 (Randomized controlled trial/ or Controlled clinical trial/ or random$.ti,ab. or randomization/ or intermethod comparison/ or placebo.ti,ab. or (compare or compared or comparison).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (open adj label).ti,ab. or ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. or double blind procedure/ or parallel group$1.ti,ab. or (crossover or cross over).ti,ab. or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. or (assigned or allocated).ti,ab. or (controlled adj7 (study or design or trial)).ti,ab. or (volunteer or volunteers).ti,ab. or human experiment/ or trial.ti.) not (((random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)) or (Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or

randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or (((case adj control$) and random$) not randomi?ed controlled).ti,ab. or (Systematic review not (trial or study)).ti. or (nonrandom$ not random$).ti,ab. or "Random field$".ti,ab. or (random cluster adj3 sampl$).ti,ab. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or "update review".ab. or (databases adj4 searched).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/))) (5266187)

6 4 and 5 (1504)

7 limit 6 to (embase and article) (519)

Search Strategy for PubMed/Medline

(31.10.2022)

Population Search Filter	#1 ("child"[MeSH Terms] OR "child*"[Title/Abstract] OR "pediatrics"[MeSH Terms] OR "paediatric"[Title/Abstract]) AND ("asthma"[MeSH Terms] OR "asthma*"[Title/Abstract])	57,914
Therapy Search Filter	#2 ("biological factors"[MeSH Terms] OR "biological factors"[Title/Abstract] OR "biological agents"[Title/Abstract] OR "antibodies, monoclonal"[MeSH Terms] OR "monoclonal antibodies"[Title/Abstract] OR "monoclonal antibody"[Title/Abstract] OR "anti-IgE antibodies"[Supplementary Concept] OR "anti-IgE antibodies"[All Fields] OR "anti ige"[Title/Abstract] OR "omalizumab"[MeSH Terms] OR "omalizumab"[Title/Abstract] OR "omalizumab's"[Title/Abstract] OR "rhuMAb-E25"[Supplementary Concept] OR "rhuMAb-E25"[Title/Abstract] OR "rhuMAb-E25"[Title/Abstract] OR "omalizumab"[MeSH Terms] OR "omalizumab"[Title/Abstract] OR "xolair"[Title/Abstract] OR "omalizumab's"[Title/Abstract] OR "mepolizumab"[Supplementary Concept] OR "mepolizumab"[Title/Abstract] OR "benralizumab"[Supplementary Concept] OR "benralizumab"[Title/Abstract] OR "reslizumab"[Supplementary Concept] OR "reslizumab"[Title/Abstract] OR "interleukin-13"[MeSH Terms] OR "interleukin-13"[Title/Abstract] OR "dupilumab"[Supplementary Concept] OR "dupilumab"[Title/Abstract] OR "tezepelumab"[Supplementary Concept] OR "tezepelumab"[Title/Abstract]) AND ("placeboes"[Title/Abstract] OR "placebos"[MeSH Terms] OR "placebos"[Title/Abstract] OR "placebo"[Title/Abstract] OR "salicylhydroxamic acid"[Supplementary Concept] OR "salicylhydroxamic acid"[Title/Abstract] OR "sham"[Title/Abstract] OR "dummies"[Title/Abstract] OR "dummy"[Title/Abstract] OR "dummy s"[Title/Abstract] OR "fake"[Title/Abstract])	65,687
Study Design Filter	#3 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[Title/Abstract] OR randomised[Title/Abstract]) OR (placebo[Title/Abstract]) OR (drug therapy[sh]) OR (randomly[Title/Abstract]) OR (trial[Title/Abstract]) OR (groups[Title/Abstract])) NOT (animals[mh] NOT humans[mh])	4,808,120
Results	1 AND 2 AND 3	489

Table 1: Study Characteristics

Trial	N Female	N randomized	Disease stage	Age (median/mean)	Mean duration of asthma (years)	Baseline predicted FEV1 (placebo arm)	Nº exacerbations in previous year (placebo arm)	Nº hospitalisations in previous year (placebo arm)	Baseline therapy (placebo arm)	Guideline Based asthma care scale	Asthma control score (placebo arm)
Jackson 2022	126, 43,44%	290	Severe asthma	10	.	93%	43% 3 or more	4% 3 or more	55% on Step 5 (fluticasone 500 mg twice daily + LABA)	American Thoracic Society and Eurpean Respiratory Society	CASI score: 6.9 (SD 2.7)
Sfezler 2022	151 43.64	346	Moderate to severe asthma	14,2	.	70%	65% had at least one exacerbation in the previous year	.	ICS total daily dose » 100mg +LABA	Gina 2020	ACQ5 2,76 (0,83)
Bacharier 2021	146 35.8	408	Moderate-to-severe asthma	8,9	.	78,4% : Type 2 Inflamatory Phenotype 77,9% more 300 Blood Eosinophils permm	47% of patients had at least one asthma exacerbation in the previous year	.	medium-dose ICS with a second controller medication (i.e., LABA, LAMA, LTRA or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller medication	Gina 2020	Score on ACQ-7-IA: 2.1 (SD 0.8)
Menzies Gow 2020	63,5% out of all participants (including non-paediatric)	82	Moderate-to-severe asthma	12 to 17	.	62,7% pre-bronchodilator	60% of the study population comprises patients who had at least two exacerbations in the 12 months before	.	20% Medium or high dose ICS +additional controller medication with or without oral glucocorticoids		ACQ-6 more than 1,5
Teach 2015	175 36,6	478	Mild-to-severe asthma	9	.	89,60%	38,3% at least one exacerbation	.	184 on Step 5 (fluticasone 500 mg and 50mg of salmeterol twice daily; During the intervention period step levels remained fixed; median adherence to asthma medication was high	Expert Panel Report-3 [EPR3]	C-ACT score 21,3

Busse 2011	177 42.2	419	Moderate to severe asthma	10,8	7	92,20%	.	52 patients had at least one hospitalization	111 on step level equal to 4 to 6 (250-500 mg fluticasone + 50mg salmeterol twice a day +/- Montelukast once a day)	NAEPP guidelines	C-ACT score in the previous month 20,7 (3,9)
Kulus 2010	81 34,4	235	Moderate or severe asthma (at least step 3)	8,6	.	82,60%	2,8 mean number of asthma exacerbations in previous year	.	Any ICS »200mg/day equivalent of fluticasone admin with dry powder inhaler	National Heart, Lung and Blood institute	.
Berger 2003	67 30%	225	Moderate to severe asthma	9,4	6,1	84,00%	2,5 mean number of asthma exacerbations in previous year	8% of patients were hospitalized for asthma treatment in previous year	All patients were switched to BDP 42ug/puff for oral inhalation twice daily (168-420ug/d)	None; all patients received same baseline therapy	21% with Severe Asthma (FEV1<65%)
Milgrom 2001	100 30%	334	Minimal asthma symptoms with mean rescue albuterol use under 2puffs/day	9,5	6,1	85%	2,2 mean number of exacerbations in previous year	9 patients were hospitalized for asthma treatment in previous year	All patients were switched to BDP 42ug/puff for oral inhalation twice daily (168-420ug/d)	None; all patients received same baseline therapy	.

Table 2: Study Characteristics (continuation)

Trial	Key inclusion criteria	Key exclusion criteria	Run-in	Co-interventions	Arm 1	Arm 1 dose	Arm 1 n	Arm 2	Arm 2 dose	Arm 2 n
Jackson 2022	- ≥2 asthma exacerbations in the prior year - peripheral blood eosinophils ≥150 cells/µl at baseline	- Cureently receiving immunotherapy or omalizumab - Omalizumab in the previous 6 months - Daily fluticasone + LABA dose ≥500 mcg twice daily	4 weeks	Dependant on treatment step. All participants on at least 250 mcg of fluticasone twice daily (Step 3)	Mepolizumab	- 6 to 11 years 40 mg - 12 to 17 years 100 mg	146	Placebo	- 6 to 11 years 40 mg - 12 to 17 years 100 mg	144
Sfezler 2022	high dose ICS therapy for >/= 6 months + a second controller; Five-Item Asthma Control Questionnaire (ACQ-5) score of ≥1.5	current use of any anti- interleukin (IL) -13 or anti-IL-4/IL-13 therapy, including lebrikizumab Use of other monoclonal antibody therapy, including omalizumab	2 weeks	ICS total daily dose » 100mg +LABA	Lebrikizumab	37.5 mg and 125 mg	229	Placebo	Matching placebo doses	117
Bacharier 2021	at least 3 month of medium-dose ICS with second controler or high dose ICS;Pre-bronchodilator FEV1≤95% of predicted normal; a severe exacerbation within 1 year prior	Baseline blood eosinophil counts of >1500 cells/µl at screening; Chronic lung disease; History of life threatening asthma; non compliance of background	4 weeks	All on ICS of medium dose with second controler	Dupilumab	less than 30Kg 100mg more than 30kg 200mg	273	Placebo	less than 30Kg 100mg more than 30kg 200mg	135
Menzies Gow 2020	at least 2 asthma exacerbation events in prior year; Morning preBD FEV1 less 90%; Daily dose more than 500mg fluticasone and an aditional controlerfor at least 3 months	Known Anaphylaxis with biological therapy; pulmonary disease other than asthma; significant infection in the 2 weeks prior; use of imunossupressive drugs in the 12 weeks before	5-6 weeks	Medium or high dose ICS +additional contrller medication with or without oral glucocorticoids	Tezepelumab	210 mg Q4W	41	Placebo	matching dose	41

Teach 2015	≥ 1 asthma exacerbations in the prior year; diagnose more than 1 year prior recruitment; positive skin test response to 1 or more perennial allergens	History of severe anaphylactic reaction(s); individuals who were enrolled in the previous ICAC trial	4-9 month	Dependant on treatment step. All participants on at least 100 mcg of fluticasone twice daily (Step 2)	Omalizumab	minimum dose 0,016mg/kg/lgE	348	Placebo	minimum dose 0,016mg/kg/lgE	89
Busse 2011	Receiving long-term asthma control therapy; have symptoms consistent with persistent asthma; have evidence of uncontrolled disease	Received systemic corticosteroids 2 weeks prior to the beginning of the study;	4 week	Conventional therapy according to the Nationa Asthma Education and Prevention Program	Omalizumab	75-375 mg (minimun monthly dose of 0,016mg/kg/lgE)	208	Placebo	Same volume as intervention	211
Kulus 2010	inadequatelly controlled asthma within the previous 2 years;igE from 30-1300IU; more than 12% increase in fev1 after bronchodilator; history of asthma exacerbationsand inadequate symptom control	Patients who received systemic corticosteroids for reasons other than asthma	8 weeks (first 4 weeks asthma medication could be adjusted and no dose adjustments were permitted during the last 4 weeks)	Any ICS »200mg/day equivalent of fluticasone admin with dry powder inhaler	Omalizumab	based on patients weight: 75-375mg	159	Placebo	matching dose	76
Berger 2003	allergic asthma well controlled for 3 months or longer with ICS; total serum IgE level between 30 and 1,300 IU/mL; (FEV1) 60%; skin prick test + for allergens	Previous treatment with omalizumab; a history of acute infectious sinusitis, respiratory tract infection, or active lung disease 1 month before trial	4-6 weeks	Albuterol SOS; baseline dose BDP (bclomethasone dipropionate) first 16 weeks and then tapered gradually 12-week	Omalizumab	150 or 300 mg every 4 weeks or 225, 300, or 375 mg every 2 weeks	116	Placebo	matching dose	109

Milgrom 2001	asthma was well controlled with ICS equivalent to 168 to 420 ug/d of beclomethasone dipropionate and broncodilator tx as needed for more than 3 months before randomization;baseline forced expiratory volume at 1 second (FEV-1) more than 60% ;igE from 30-1300IU; diagnosis with at least 1 year	previous treatment with omalizumab; known hypersensitivity to any study drug; active lung disease	4-6 weeks; then a stable steroid phase (16 weeks) and a steroid phase reduction (12 weeks	controlled ics equivalent 168-420 mg of BDP and brochodilator	Omalizumab	150-300mg every 2 weeks or 375mg every 2 weeks	225	Placebo	matching dose	109

Table 3: Methodological Characteristics

Trial	Objective	Masking	Centers	Nation	Setting	Control	Funding	Phase	Primary endpoint	Follow-up (mean/median)
Jackson 2022	Not reported	Triple	Multi-center	International	Out-patient	Active + control	Industry	2	Asthma exacerbations	52 weeks
Szefler 2022	Not reported	Double	Multi-center	International	Out-patient	Active + control	Industry	3	Asthma exacerbations	52 weeks
Bacharier 2021	Superiority	Triple	Multi-center	International	Out-patient	Active + control	Industry	3	Annualized Rate of Sev	52 weeks
Menzies Gow 2020	Superiority	Triple	Multi-center	International	Out-patient	Active + control	Industry	3	Asthma exacerbations	52 weeks
Teach 2015	Superiority	Triple	Multi-center	Single-nation	Out-patient	Active + control	Industry	4	Occurrence of one or m	90 days
Busse 2011	Not reported	Double	Multi-center	Single-nation	Out-patient	Active + control	Unclear	4	Maximum Number of A	jacks
Kulus 2010	Superiority	Triple	Multi-center	International	Out-patient	Active + control	Industry	3	Asthma exacerbations	52 weeks
Berger 2003	Not reported	Triple	Multi-center	International	Out-patient	Active + control	Industry	3	Safety and Tolerability	28 weeks
Milgrom 2001	Not reported	Double	Single-center	Single-nation	Out-patient	Active + control	Industry	3	safety and steroid spar	28 weeks

Risk of Bias Tables

Unique ID	Jackson 2022	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Mepolizumab	**Comparator**	Placebo	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome		**Results**		**Weight**	290

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	Szefler 2022	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Lebrikuzumab	**Comparator**	Placebo	**Source**	Journal article(s); Trial protocol; Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome		**Results**		**Weight**	346

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN	Out of 346 randomly assigned patients, results are presented for only 194. 44% of patients data are lost
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY	Reasons for lost of patients are presented on the article
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Bacharier 2021	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Dupilumab	**Comparator**	Placebo	**Source**	Journal article(s); Trial protocol; Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome		**Results**		**Weight**	408

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	Menzies Gow 2020	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Tezepelumab	**Comparator**	Placebo	**Source**	Journal article(s); Trial protocol; Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome		**Results**		**Weight**	82

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	Teach 2015	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Omalizumab	**Comparator**	Placebo	**Source**	Journal article(s); Trial protocol; Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome		**Results**		**Weight**	478

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Busse 2011	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Omalizumab	**Comparator**	Placebo	**Source**	Journal article(s); Trial protocol; Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome		**Results**		**Weight**	419

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Kulus 2010	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Omalizumab	**Comparator**	Placebo	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome		**Results**		**Weight**	235

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Milgrom 2001	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Omalizumab	**Comparator**	Placebo	**Source**	Journal article(s);
Outcome		**Results**		**Weight**	334

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
	5.3 ... multiple eligible analyses of the data?	NI	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	Berger 2003	**Study ID**		**Assessor**	IF
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Omalizumab	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome		**Results**		**Weight**	225

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	