Sex differences in adult asthma and COPD therapy: a systematic review

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Abstract
Background: Although asthma is more prevalent in women and the prevalence of COPD is increasing in women, the current international recommendations for the management and prevention of asthma and COPD provide no sex-related indication for the treatment of these diseases. Therefore, we systematically reviewed the evidence across literature on the sex-related effectiveness of asthma and COPD therapy.

Methods: This systematic review has been registered in PROSPERO and performed according to PRISMA-P. The PICO framework was applied for the literature search strategy: “patient problem” included adult patients suffering from asthma or COPD, “Intervention” regarded the pharmacological treatments for asthma or COPD, “Comparison” was vs. baseline, active controls, or placebo, “Outcome” was any difference sex-related in the effectiveness of interventions.

Results: In asthma 44% of the evidence reported that men responded better than women to the therapy, whereas this percentage was 28% in COPD. ICS was generally less effective in women than in men to treat asthma, and consistent evidence suggests that in asthmatic patients ICS/LABA/LAMA combination may be equally effective in both men and women. Due to the inconsistent available evidence, it is not possible to identify specific treatments whose effectiveness is related to sex difference in COPD patients.

Conclusions: There is a strong need of investigating the sex-related impact of asthma and COPD treatments. Pre-specified analyses in men and women should be planned in future trial protocols, a necessary condition that should be requested also by the regulatory agencies to overcome the anachronistic “one-size-fits-all” approach to therapeutics associated with suboptimal outcomes for patients.

Keywords: Asthma, COPD, Gender, Sex, Systematic review, Therapy

Background
Current data indicate that asthma and chronic obstructive pulmonary disease (COPD) affect together more than 600 million people worldwide and caused more than 3.5 million deaths per year [1–4]. The absolute number of patients suffering from asthma and COPD is increasing as the global population grows, and a relevant percentage of patients has been found to have suboptimal control of symptom burden [5].

Despite asthma is more prevalent in women and the prevalence of COPD is increasing in women [6, 7], and considering that cumulating evidence has highlighted the key pivotal role of sex differences in non-communicable diseases (NCDs) [8], the current international recommendations for the management and prevention of asthma and COPD [1, 2] do not provide any sex-related indication for the treatment of these diseases. Certainly, it may be also assumed that the lack of sex-specific recommendations for the treatment of asthma and COPD could be because no real difference in effectiveness exists but, unfortunately, to date it is not known whether this
hypothesis is true [9]. In any case, it seems that both sex, assessed as male or female according to biological attributes, and gender, referred to social roles, behaviours, and expressions of identity, may significantly modulate the pharmacological response to asthma and COPD treatments [7, 10].

In this uncertain context, the aim of this article was to systematically review the evidence across literature on the sex-related effectiveness of pharmacotherapy in the treatment of asthma and COPD.

Indeed, a large body of evidence suggests that integrating data from randomized controlled trials (RCTs) and observational studies in systematic reviews and/or meta-analyses regarding complex interventions, such as the management of chronic obstructive pulmonary disorders according to the sex, may improve the prediction of patient responses to pharmacological therapies, resulting of high value and interest to patients, clinicians, policymakers, and other healthcare stakeholders [11, 12]. Moreover, including information also from observational studies may improve the inference based on RCTs [13]. Interestingly, these advantages of adding observational studies to RCTs to bring complementary healthcare information seems to be independent from the quality of the studies included [12]. Effectively, considering that it is unusual to find sufficient evidence from RCTs to answer all key questions in a systematic review, there is no a priori reason to exclude observational studies from a qualitative synthesis [13, 14]. After all, the greatest level in the new hierarchy of evidence is reached when both RCTs and observational studies exist with consistent findings [15].

Therefore, moving from this solid background and considering that the impact of sex differences in adult asthma and COPD therapy is a relevant but usually neglected topic, we carried out a systematic review by including both RCTs and observational studies.

**Methods**

**Review question**

The question of this systematic review was to assess sex-related differences in the effectiveness of pharmacological treatments for asthma and COPD.

**Search strategy**

This systematic review has been registered to the international prospective register of systematic reviews (PROSPERO, submission ID: 307060), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [16]. The PRISMA 2020 flow diagram is shown in Fig. 1. This study satisfied all the recommended items reported by the PRISMA-P checklist [16]. A comprehensive literature search was performed for clinical trials assessing potential sex differences regarding the effectiveness of pharmacological treatments for asthma or COPD.

In this regard, the PICO (Patient problem, Intervention, Comparison, and Outcome) framework was applied to develop the literature search strategy, as previously reported [17]. Namely, the “patient problem” included adult patients suffering from asthma or COPD; the “intervention” regarded the administration of different pharmacological treatments for asthma or COPD; the “comparison” was performed with respect to baseline, active controls, or placebo (PCB); the assessed “outcome” was any difference related to sex in the effectiveness of pharmacological treatments for asthma and COPD.

The search was performed in ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, EU Clinical Trials Register, MEDLINE, Scopus, and Web of Science, in order to provide for relevant studies written in English and published up to January 3rd, 2022. The research string was as follows: (sex[TI] OR gender[TI]) AND (asthma OR COPD) AND (("sex"[TI] OR "gender"[TI]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "asthmas"[All Fields] OR "asthma s"[All Fields] OR ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]))) AND (clinicaltrial[Filter] OR observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]). Citations of previous published reviews and commentaries were checked to select further pertinent studies, if any [6, 7, 18–22]. Literature search results were uploaded to Ep doorway 4 (EPPI-Centre Software, London, UK), a web-based software for managing and analysing data in literature reviews that facilitates collaboration among reviewers during the study selection process.

**Study selection**

Clinical trials that enrolled adult asthmatic or COPD patients and assessing sex-related differences in the effectiveness of pharmacological treatments for asthma or COPD were included in the systematic review. Two reviewers independently examined the studies, and any difference in opinion concerning the selection of relevant studies from literature searches and databases was resolved by consensus.

**Data extraction**

Data from included clinical trials were extracted from published papers and/or supplementary files. Data
were checked for study references and characteristics, number of analysed patients, treatments and comparators with doses of medications, regimen of administration, and type of inhaler, main inclusion criteria, age, sex, smoking habit, forced expiratory volume in the 1st second (FEV₁), exacerbation rate, any efficacy outcome measurements to detect potential differences between men and women, and study quality assessment via the Jadad Score [23], Cochrane Risk of Bias 2 (RoB 2) [24], Newcastle–Ottawa Scale (NOS) score [25], and Joanna
Briggs Institute (JBI) Critical Appraisal Checklist Tool [26].

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [27].

Endpoint
The endpoint of this systematic review was to assess sex-related differences in the effectiveness of pharmacological treatments used for asthma and COPD.

Strategy for data synthesis
Data from original papers were extracted and reported via qualitative synthesis. Parts of Whole analysis via 10 × 10 dot plot graph was used to report the amount of evidence concerning the impact of sex on the response to the overall treatments in asthma and COPD. Bar Charts were used to show the response to pharmacological treatments in asthma and COPD according to specific outcomes and number of evidences.

Quality of studies and risk bias
The summary of the risk of bias for each included randomized trial was analyzed via the Cochrane RoB 2 [24] and Jadad score [23]. The weighted assessment of the overall risk of bias was analyzed via the Cochrane RoB 2 [24] by using the robvis visualization software [28, 29].

The Jadad score, with a scale of 1–5 (score of 5 being the best quality), used to assess the quality of the clinical trials concerning the likelihood of bias related with randomization, double blinding, withdrawals, and dropouts. The quality of studies was assessed as follows: total score ≤ 2, low quality; total score = 3, medium quality; total score ≥ 4 high quality.

The NOS was used to assess the quality of observational cohort studies [25]. According to NOS, a study can be awarded with a maximum of one star for each item within the “Selection” and “Outcome” and a maximum of two stars can be given for “Comparability” [25]. In the present systematic review, the NOS quality assessment score was established to be in the range between zero and a maximum of nine stars. Studies reporting a NOS score ≥ 7 were considered of high quality, whereas those reporting a NOS score ≤ 6 were considered of low quality. For the NOS category “Outcome”, a follow-up period of at least ≥6 months was considered adequate to obtain the outcomes of interest from the included studies [30].

The methodological quality of observational cross-sectional studies was evaluated by using the JBI Critical Appraisal Checklist Tool for analytical cross-sectional studies [26]. The checklist consisted of eight question items assessing the inclusion criteria for the definition and detailed description of the sample, use of valid and reliable way to measure the exposure, use of objective and standard criteria to measure the condition, identification, and strategies to deal with confounding factors, use of a valid and reliable way to measure outcomes, and suitability of statistical analysis. In the present systematic review, each item of the JBI checklist was rated as “yes” and given 1 point and “no”, “unclear” or “not applicable” and given 0 points. The quality assessment score was calculated on the proportion of “yes” responses for the possible maximum score and judges at high risk, moderate risk or low risk of bias in agreement with the percentage of the achieved score, that was ≤ 49%, 50–69%, or ≥ 70%, respectively. Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

Results
Study characteristics
Of the 90 potentially relevant records identified in the initial search, 32 studies were deemed eligible for a qualitative synthesis (Table 1). This systematic review included data obtained from studies performed on patients with asthma [31–39], COPD [40–61], and populations in which both asthmatic and COPD patients were included [62].

Overall, 6 studies [31, 34, 46, 55, 57, 60] RCTs, 4 studies [32, 33, 58, 62] were retrospective observational, 3 studies [36, 38, 40] were prospective observational, and 1 study [35] was focused on pharmacodynamics (PD). Eight [41, 44, 48, 49, 52, 59] studies were post-hoc analyses of RCTs and another one [37] of an observational study, 6 studies [39, 42, 45, 50, 51, 54] were pooled analyses of RCTs, 2 studies [43, 56] were subgroup analyses of RCTs, 1 study [61] was an extended analysis of a RCT, and 1 study [47] was a sensitivity analysis of a RCT. One study [53] reported an analysis of trial data released by the US Food and Drug Administration (FDA).

Tables 2 and 3 summarize the results of the studies in which a sex-related difference in the effectiveness of asthma and COPD therapies has been assessed.

Sex differences in asthma therapy
ICS
Intermittent pulsed therapy at 2 week-intervals with fluticasone propionate (FP) 2000 μg once daily (QD) for 6 weeks induced a short-term benefit on airway responsiveness that was lower in treatment-naïve women than in men with mild asthma, by producing respectively 1.2 vs. 3.2 doublings in the provocative dose of methacholine causing a 20% fall in FEV1 (PD20) (P < 0.05) [31].

In a cross-sectional French study on asthmatic patients [32], women treated with inhaled corticosteroids (ICS) in the past year were at significant (P < 0.05) greater risk
| Study, year and reference | Number identifier | Study characteristics | Treatment duration (months) | Number of analyzed patients | Drugs, doses, and regimen of administration | Route of administration | Inhaler device (brand) | Patients’ characteristics |
|---------------------------|-------------------|----------------------|-----------------------------|-----------------------------|---------------------------------------------|------------------------|-----------------------|--------------------------|
| Nerpin et al. 2021 [36]   | NA                | Observational, multicenter, prospective, population-based cohort study based on the 3rd European Community Respiratory Health Survey (ECRHS III) | 1 day                       | 651                         | SALB 200 μg single dose                     | Oral inhalation        | MDI (NA)              | Asthma (≥ 1 asthma-related symptom, including wheeze, nocturnal chest tightness or attacks of breathlessness following activity, at rest or at night and/or reported current use of ICSs in the previous year) |
| Harvey et al. 2020 [38]   | ACTRN12618001497291 | Observational, multicenter, prospective, post-marketing surveillance study based on the Australian Mepolizumab Registry (AMR) | 12.0                        | 309                         | Mepolizumab 100 mg Q4W                      | SC injection           | /                     | Severe uncontrolled eosinophilic asthma (FEV1 ≤ 80% predicted; confirmed variable obstruction: 1) FEV1 reversibility ≥ 12% and ≥ 200 mL within 30 min after administration of salbutamol 200–400 μg or 2) AHR defined as ≥ 20% decline in FEV1 during a direct bronchial provocation test or > 15% decline during an indirect test or 3) PEF variability of > 15% between the two highest and two lowest PEF rates during 14 days; ACQ-5 score ≥ 2 in the previous month and 1) ≥ 1 hospitalization for a severe asthma exacerbation or 2) ≥ 1 severe asthma exacerbation requiring use of OCSs initiated or increased for ≥ 3 days or parenteral corticosteroids prescribed/supervised by a physician) |
| Study, year and reference | Number identifier | Study characteristics | Treatment duration (months) | Number of analyzed patients | Drugs, doses, and regimen of administration | Route of administration | Inhaler device (brand) | Patients' characteristics |
|--------------------------|-------------------|----------------------|-----------------------------|-----------------------------|--------------------------------|------------------------|----------------------|--------------------------|
| Ohar et al. 2020 [45]    | NCT02347761 (GOLDEN 3), NCT02347774 (GOLDEN 4) | Pooled analysis of 2 replicate Phase III, multicenter, randomized, double-blind, PCB-controlled, parallel group | 3.0                          | 861                          | GLY 25 μg BID vs. PCB               | Oral inhalation       | eFlow® nebulizer       | Moderate to severe COPD (post-bronchodilator FEV₁ ≤ 80% predicted and FEV₁/FVC < 0.7) |
| Colombo et al. 2019 [37] | NA                | Post-hoc analysis of the observational, multicenter, non-controlled, cohort PROXIMA study including a cross-sectional and prospective longitudinal phases (omalizumab) was administered exclusively in the longitudinal phase | 12.0                         | 99 (in the longitudinal phase) | Add-on omalizumab 75—600 mg Q4W | SC injection         | /                    | Severe allergic asthma   |
| D'Urzo et al. 2019 [51] | NCT01462942 (ACLI-FORM), NCT01437397 (AUGMENT) | Pooled analysis of 2 Phase III, multicenter, randomized, double-blind, active-and PCB-controlled, parallel group studies | 24.0                        | 2684                         | ACL/FOR 400/12 μg BID vs. ACL 400 μg vs. FOR 12 μg vs. PCB | Oral inhalation       | DPI (Genuair™/Pressair®) |
| Wedzicha et al. 2019 [52] | NCT01782326 (FLAME) | Post-hoc analysis of the randomized, double-blind, double-dummy, active-controlled, parallel group FLAME trial | 12.0                          | 3362                         | IND/GLY 110/50 μg QD vs FP/SAL 50/500 μg BID | Oral inhalation       | IND/GLY: DPI (Breezhaler®), FP/SAL: DPI (Accuhaler®) | Moderate to severe COPD (post-bronchodilator FEV₁ ≥ 25% and < 60% predicted and FEV₁/FVC < 0.7; ≥ 1 exacerbation in the previous year) |
| Martinez et al. 2018 [54] | NCT01329029 (REACT), NCT01443845 (RE2SPOND) | Pooled analysis of 2 Phase IV, multicenter, randomized, double-blind, PCB-controlled, parallel group studies | 12.0                          | 4287                         | Add-on roflumilast 500 μg QD vs. PCB | PO                    | /                    | Severe or very severe COPD (post-bronchodilator FEV₁ < 50% predicted and FEV₁/FVC < 0.7) |
| Study, year and reference | Number identifier | Study characteristics | Treatment duration (months) | Number of analyzed patients | Drugs, doses, and regimen of administration | Route of administration | Inhaler device (brand) | Patients’ characteristics |
|---------------------------|-------------------|----------------------|----------------------------|-----------------------------|---------------------------------------------|------------------------|-----------------------|--------------------------|
| Li et al. 2017 [44]       | NA                | Post-hoc analysis of the multicenter, randomized, PCB-controlled, parallel-group LHS study | 60.0                       | 5887                        | IB 72 μg TID vs. PCB                         | Oral inhalation        | NA                    | Mild to moderate COPD (post-bronchodilator FEV₁ ≥ 55% and ≤ 90% predicted and FEV₁/FVC < 0.7) |
| Tsiliogianni et al. 2017 [50] | NCT01120717 (ENLIGHTEN), NCT0120188 (SHINE), NCT01120691 (SPARK), NCT01315249 (ILLUMINATE), NCT01285492 (ARISE), NCT01709903 (LANTERN) | Pooled analysis of 6 randomized, PCB- or active-controlled, parallel-group studies (data from the ARISE on Japanese population only) | 26.0–64.0                  | 6108                                       | IND/GLY 100/50 μg QD vs. FP/SAL 500/50 μg BID vs. GLY 50 μg QD vs. TIO 18 μg QD vs. PCB | Oral inhalation        | IND/GLY: DPI (Breezhaler®), FP/SAL: DPI (Accuhaler®) | Moderate to severe COPD or severe to very severe COPD in the SPARK (post-bronchodilator FEV₁ ≥ 30% and < 80% predicted [except SPARK where patients were having post-bronchodilator < 50% predicted], and a FEV₁/FVC < 0.7; history of ≤ 1 exacerbation at baseline for inclusion into the LANTERN and a history of ≥ 1 exacerbation in the previous year for inclusion in the SPARK) |
| Kerstjens et al. 2016, PrimoTinAsthma® [34] | NCT00722538, NCT0076984 | Two Phase III, randomized, double-blind, PCB-controlled, parallel group | 48.0                       | 912                                         | Add-on TIO 5 μg QD vs. PCB to ICS/LABA | Oral inhalation        | SMI (Respimat®) | Severe symptomatic asthma post-bronchodilator FEV₁ ≤ 80% predicted and FEV₁/FVC ≤ 0.7 measured 30 min after inhaling 400 μg of salbutamol at screening, daily treatment with ≥ 800 μg of BUD or equivalent dose of another ICS + LABA for ≥ 4 weeks before screening ≥ 1 exacerbation requiring treatment with SCSs in the previous year; ACQ-7 score ≥ 1.5 |
### Table 1 (continued)

| Study, year and reference | Number identifier | Study characteristics | Treatment duration (months) | Number of analyzed patients | Drugs, doses, and regimen of administration | Route of administration | Inhaler device (brand) | Patients' characteristics |
|--------------------------|-------------------|----------------------|-----------------------------|-----------------------------|---------------------------------------------|-------------------------|------------------------|--------------------------|
| Han et al. 2014 [56]     | NA                | Subgroup analysis of a multicenter, prospective, randomized, double-blind, PCB-controlled, parallel group study (NCT00325897) | 12.0                        | 1113                        | Azithromycin 250 mg QD vs. PCB | PO                     | /                      | COPD (post-bronchodilator FEV<sub>1</sub> < 80% predicted and FEV<sub>1</sub>/FVC < 0.7) |
| Yu et al. 2014 [53]      | NA                | Analysis of trial data released by the US FDA | ≤ 12.0                     | NA                          | Add-on roflumilast 500 μg QD vs. PCB | PO                     | /                      | Moderate to severe COPD |
| Albert et al. 2011 [55]  | NCT00325897       | Multicenter, prospective, randomized, double-blind, PCB-controlled, parallel group | 12.0                        | 1142                        | Azithromycin 250 mg QD vs. PCB | PO                     | /                      | COPD (post-bronchodilator FEV<sub>1</sub> < 80% predicted and FEV<sub>1</sub>/FVC < 0.7) |
| Celli et al. 2011 [61]   | NCT00268216 (TORCH) | Extended-analysis of the Phase III, randomized, double-blind, PCB-controlled, parallel group TORCH study | 36.0                        | 6112                        | FP 500 μg BID vs. SAL 50 μg BID vs. PCB | Oral inhalation | DPI (Accuhaler<sup>®</sup>) | COPD (pre-bronchodilator FEV<sub>1</sub> < 60% predicted and pre-bronchodilator FEV<sub>1</sub>/FVC < 0.7; reversibility of FEV<sub>1</sub> to 400 μg salbutamol of < 10% of predicted) |
| Tashkin et al. 2011 [60] | NCT00285012       | Multicenter, Phase III, randomized, double-blind, PCB-controlled, parallel group | 3.0                         | 499                         | Varenicline 0.5 mg QD for 3 days, 0.5 mg BID for 4 days, then 1 mg BID until end of the study | PO                     | /                      | Mild to moderate COPD (post-bronchodilator FEV<sub>1</sub> ≥ 50% and FEV<sub>1</sub>/FVC < 0.7) |
| Tashkin et al. 2011 [49] | NA                | Post-hoc analysis of a multicenter, randomized, double-blind, active-controlled, parallel group study | 3.0                         | 255                         | FOR 12 μg BID + TIO 18 μg QD vs. TIO 18 μg QD | Oral inhalation | DPI (NA)               | COPD (post-bronchodilator FEV<sub>1</sub> > 30% and < 70% predicted and FEV<sub>1</sub>/FVC < 0.7) |
| Lopez-Varela et al. 2010, PLATINO [58] | NA             | Multicenter, cross-sectional, population-based survey | 1 day                       | 759                         | SALB 200 μg single dose | Oral inhalation | NA                    | COPD                     |
### Table 1 (continued)

| Study, year and reference | Number identifier | Study characteristics | Treatment duration (months) | Number of analyzed patients | Drugs, doses, and regimen of administration | Route of administration | Inhaler device (brand) | Patients’ characteristics |
|--------------------------|-------------------|----------------------|----------------------------|-----------------------------|---------------------------------------------|----------------------------|--------------------------|--------------------------|
| Tashkin et al. 2010 [43] | NCT00144339 (UPLIFT) | Subgroup analysis of the Phase III, multicenter, randomized, double-blind, PCB-controlled, parallel group UPLIFT study | 48.0 | 5992 | TIO 18 μg QD vs. PCB | Oral inhalation | DPI (HandiHaler®) | COPD (post-bronchodilator FEV₁ < 70% predicted and FEV₁/FVC ≤ 0.7) |
| Siroux et al. 2009 [32] | NA | Observational, cross-sectional study using data from the case-control and family-based EGEA2 study | 12.0 | 501 | ICS | Oral inhalation | NA | Current asthma |
| Celli et al. 2008 [48] | NCT00268216 (TORCH) | Post-hoc analysis of the Phase III, randomized, double-blind, PCB-controlled, parallel group TORCH study | 36.0 | 5,343 | FP/SAL 500/50 μg BID vs. FP 500 μg BID vs. SAL 50 μg BID vs. PCB | Oral inhalation | DPI (Accuhaler®) | COPD (pre-bronchodilator FEV₁ < 60% predicted and pre-bronchodilator FEV₁/FVC ≤ 0.7; reversibility of FEV₁, to 400 μg salbutamol of <10% of predicted) |
| Calverley et al. 2007, TORCH [46] | NCT00268216 | Phase III, randomized, double-blind, PCB-controlled, parallel group | 36.0 | 6112 | FP/SAL 500/50 μg BID vs. FP 500 μg BID vs. SAL 50 μg BID vs. PCB | Oral inhalation | DPI (Accuhaler®) | COPD (pre-bronchodilator FEV₁ < 60% predicted and pre-bronchodilator FEV₁/FVC ≤ 0.7; reversibility of FEV₁, to 400 μg salbutamol of <10% of predicted) |
| Soriano et al. 2007, ISEEC study [42] | NA | Pooled analysis of 7 randomized, double-blind, PCB-controlled, parallel group studies | 12.0–36.0 | 3911 | ICS use (triamcinolone 1200 μg QD; BUD 800—867 μg QD; FP 1000 μg QD) | Oral inhalation | NA | Moderate to severe COPD |
| Dales et al. 2006 [62] | NA | Observational study in primary-care settings | 1 day | 187 | SALB 200 μg single dose | Oral inhalation | NA | COPD and asthma |
| Dijkstra et al. 2006 [33] | NA | Observational, retrospective, cohort study | 23 years of follow-up | 122 | ICS vs. no ICS use | Oral inhalation | NA | Moderate to severe asthma |
| Study, year and reference | Number identifier | Study characteristics | Treatment duration (months) | Number of analyzed patients | Drugs, doses, and regimen of administration | Route of administration | Inhaler device (brand) | Patients' characteristics |
|--------------------------|-------------------|----------------------|-----------------------------|-----------------------------|---------------------------------------------|-------------------------|------------------------|--------------------------|
| Watson et al. 2006 [41]  | NA                | Post-hoc analysis of the multicenter, randomized, double-blind, PCB-controlled, parallel group EUROSCOP study | 36.0                         | 1128                        | BUD 400 μg BID vs. PCB                      | Oral inhalation         | DPI (Turbuhaler®)      | Mild to moderate COPD (post-bronchodilator FEV1 50–100% and FEV1/FVC < 0.7; <10% predicted increase in FEV1 after inhalation of 1 mg terbutaline) |
| Anthonisen et al. 2005 [59] | NA                | Post-hoc analysis of a selected cohort from the multicenter, randomized, PCB-controlled, parallel-group LHS study | 11 years                     | 4194                        | Isoproterenol 200 μg                       | Oral inhalation         | MDI (NA)               | COPD (post-bronchodilator FEV1 ≥ 55 and ≤ 90% predicted and FEV1/FVC < 0.7) |
| Bousquet et al. 2005 [39] | NA                | Pooled analysis of 7 randomized, double-blind, PCB-controlled, parallel-group studies and two randomized, open-label, active-controlled, parallel group studies | 5.5–12.0                     | 4308                        | Add-on omalizumab at least 0.016 mg/kg per IU/mL of sIgE Q2W or Q4W vs. PCB or current asthma therapy without omalizumab | SC injection            | /                      | Severe persistent asthma |
| Schermer et al. 2004 [46] | NA                | Prospective, clinical-practice setting, unblinded study of the ICS washout phase of the COOPT trial | 3.0                          | 201                         | ICS discontinuation (FP, BUD, or BDP)      | Oral inhalation         | NA                     | COPD (post-bronchodilator FEV1 < 90% predicted or FEV1/FVC < 0.88 < 0.89 for women) |
| Vestbo et al. 2004 [47]  | NA                | Sensitivity analysis of the multicenter, randomized, double-blind, PCB-controlled, parallel group TRISTAN study | 12.0                         | 719                         | FP/SAL 500/50 μg BID vs. PCB                | Oral inhalation         | DPI (Advair Diskus®)   | COPD (pre-bronchodilator FEV1 ≥ 25 and ≤ 70% predicted and FEV1/FVC < 0.7; reversibility < 10% predicted FEV1) |
| Convery et al. 2000 [31] | NA                | Randomized, double-blind PCB-controlled, parallel group | 1.5                          | 52                          | FP 2000 μg QD vs. PCB                       | Oral inhalation         | pMDI (NA)              | Mild asthma (treatment-naïve patients) |
Table 1 (continued)

| Study, year and reference | Number identifier | Study characteristics | Treatment duration (months) | Number of analyzed patients | Drugs, doses, and regimen of administration | Route of administration | Inhaler device (brand) | Patients' characteristics |
|---------------------------|-------------------|----------------------|-----------------------------|-----------------------------|---------------------------------------------|-------------------------|------------------------|--------------------------|
| Lima et al. 2000 [35]     | NA                | PD study             | 1 day                       | 30                          | SALB 8 mg single dose                      | PO                     | /                      | Moderate asthma          |
| Kanner et al. 1994 [57]   | NA                | Multicenter, randomized, PCB-controlled, parallel-group | 60.0                        | 5662                        | Smoking cessation + IB vs. smoking cessations + PCB | IB: oral inhalation    | NA                     | COPD (post-bronchodilator FEV₁ ≥ 55% and ≤ 90% predicted and FEV₁/FVC < 0.7) |

| Age (years) | Male (%) | Current smokers (%) | Post bronchodilator FEV₁ (% predicted) | Evaluated outcomes | Jadad score | NOS Quality Assessment | JBI checklist Tool |
|-------------|----------|---------------------|--------------------------------------|--------------------|-------------|------------------------|-------------------|
| 53.7        | 39.3     | 149                 | 87.3                                 | Lung function      | /           | ***                    | NA                |
| 59.6        | 42.4     | 0.6                 | 62.7                                 | Disease control    | /           | ****                   | NA                |
| 63.5        | NA       | 52.5                | 52.5                                 | Lung function, exacerbations, QoL, and rescue medication use | All RCTs: 5 | **                     | 5                 |
| 51.7        | 37.4     | 5.1                 | NA                                   | Disease control, disease perception, and QoL | /           | ****                   | NA                | ** 6 |
| 63.6        | 60.0     | 49.2                | NA                                   | Lung function, exacerbations, and dyspnea | AUGMENT: 4, ACLIFORM: 5 | / | /|
| 63.9        | 76.0     | 42.6                | 44.7                                 | Exacerbations, lung function, QoL, rescue medication use | FLAME: 5 | / | / |
| 64.6        | 71.3     | 41.3                | 34.11                                | Exacerbations      | REACT: 5, RESPOND: 4 | / | / |
| 48.5        | 62.9     | 1000                | NA                                   | Lung function      | LHS: 3      | / | / |
| 63.1        | 77.2     | 41.6                | NA                                   | Lung function, QoL, rescue medication use | All RCTs: 5 | / | / |
| 53.0        | 39.6     | 0.0                 | NA                                   | Lung function, exacerbations, disease worsening | PrimoTinAsthma®: 5 | / | / |
| 65.5        | 59.0     | 220                 | 39.5                                 | Exacerbations      | NCT00325897: 4 | / | / |
| NA          | NA       | NA                  | NA                                   | Benefit-harm index | NA          | / | / |
| 65.5        | 59.0     | 22.0                | 39.5                                 | Exacerbations      | 4           | / | / |
| 65.0        | 75.8     | 43.0                | 44.3                                 | Exacerbations, QoL, and mortality | TORCH: 5 | / | / |
| 57.2        | 62.4     | 1000                | 70.0                                 | Smoking cessation   | 3           | / | / |
| ≥ 400       | 66.5     | 47.5                | NA                                   | Lung function      | RCT: 5      | / | / |
| 64.2        | 52.3     | 360                 | NA                                   | Acute broncho-reversibility | /           | / | / |
| 63.8        | 74.6     | 32.0                | 48.0                                 | Lung function, exacerbations, QoL, and mortality | UPLIFT: 5 | / | / |

| Selection | Comparability | Outcome | Total |
|-----------|---------------|---------|-------|
|           |               |         |       |

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| Age (years) | Male (%) | Current smokers (%) | Post bronchodilator FEV₁ (%) predicted | Evaluated outcomes | Jadad score | NOS Quality Assessment | JBI checklist Tool |
|------------|----------|---------------------|--------------------------------------|--------------------|-------------|-----------------------|-------------------|
| 39.2       | 50.9     | 26.3                | 94.9                                 | Lung function, exacerbations, disease symptoms | /           | Low bias              |                   |
| 64.9       | 76.3     | 44.3                | 44.7                                 | Lung function      | TORCH: 5    | /                     | /                 |
| 65.0       | 75.8     | 43.0                | 44.3                                 | Mortality          | 5           | /                     | /                 |
| 58.3       | 70.8     | 73.0                | 60.3                                 | Lung function      | 7 RCTs: between 3 and 5 | / | / | / | / |
| 59.0       | 38.0     | NA                  | NA                                   | Bronchoreversibility | /           | /                     | /                 |
| 28.0       | 58.0     | 45.0                | 85.0                                 | Lung function      | /           | **** NA **             | 6 /               |
| 52.5       | 72.3     | 100.0               | 80.2                                 | Disease symptoms   | EUROSCOP: 3  | /                     | /                 |
| 50.1       | 61.9     | 25.5                | 78.5                                 | Bronchoreversibility | LHS: 3      | /                     | /                 |
| 41.3       | 40.8     | NA                  | 70.2                                 | Exacerbations      | 7 RCTs: between 2 and 3 | / | / | / | / |
| 60.6       | 68.0     | 49.0                | 65.6                                 | Adverse respiratory outcome | /           | **** NA ***            | 7 /               |
| 62.5       | 75.0     | 51.5                | NA                                   | Lung function, exacerbations, QoL | TRISTAN: 5   | /                     | /                 |
| 32.5       | 59.6     | 48.1                | 101.2                                | Lung function      | 2           | /                     | /                 |
| 18.0–50.0  | 53.3     | 0.0                 | 92.8                                 | Lung function      | NA          | /                     | /                 |
| 48.5       | 62.8     | 100.0               | 75.0                                 | Lung function      | 3           | /                     | /                 |

*indicates one star given to the “Selection”, “Comparability”, and “Outcome” categories according to the star-based NOS scoring system employed to assess the quality of each observational study, as detailed in the section “Quality of studies and risk of bias”. /: data not evaluable; ACL aclidinium, ACQ Asthma Control Questionnaire, AHR airway hyperresponsiveness, BDP beclomethasone dipropionate, BID bis in die, twice-daily, BUD budesonide; COPD chronic obstructive pulmonary disease, DPI dry powder inhaler; FDA Food and Drug Administration, FEV₁ forced expiratory volume in the 1st second, FP fluticasone propionate, FOR formoterol, PVC forced vital capacity, GLY glycopyrronium, IB ipratropium bromide; ICS inhaled corticosteroid, IND indacaterol, JBI Joanna Briggs Institute, MDI metered dose inhaler; NA not available, NOS Newcastle–Ottawa Scale, OCS oral corticosteroid, PD₅₀ Provocative concentration of methacholine causing a 20% fall in FEV₁; PCB placebo, PD pharmacodynamics, PEF peak expiratory flow, PK pharmacokinetics; pMDI pressurized metered dose inhaler; PO oral administration; Q2W once every 2 weeks; Q4W once every 4 weeks; QD quaque die, once-daily; QoL quality of life; SAL salmeterol, SALB salbutamol; SC subcutaneous, SMI soft mist inhaler; TIO tiotropium bromide.
for uncontrolled asthma than men. Men treated with ICS showed a borderline significant reduction in the risk for severe exacerbation (P = 0.05) and had a lower frequency of symptoms than women (odds ratio [OR] 0.30, 95% confidence interval [95%CI] 0.15–0.59; P < 0.001) [32].

In moderate to severe asthmatic men, treatment with ICS over a period of 23 years reduced the annual decline in FEV₁ of 20.6 mL/year compared to the time before starting with ICS (P < 0.05), but this effect was not observed in women [33]. ICS use induced an improvement of 36.8 mL/year in the annual decline of FEV₁ only in men smoking < 5 pack/years (P < 0.01) and the difference between sexes was significant (P < 0.05) [33]. In patients smoking ≥ 5 pack/years, no change in the decline of FEV₁ was observed in both men and women [33]. A greater daily ICS dose was associated with a minor decline in FEV₁ in men (P < 0.01), an effect not observed in women [33].

**SABA**

In a study focusing on the PD response to a single-dose of salbutamol (SALB) 8 mg administered to moderate asthmatic patients [35], salbutamol increased FEV₁ from baseline in men (+620 mL, range 110–3300; P < 0.05) and women (+310 mL, range 100–770; P < 0.05), as well as FEV₁% predicted in men (13.5%, range 1–76; P < 0.05) and women (12%, range 4–24; P < 0.05) [35]. The mean plasma concentration of SALB at which maximal bronchodilation was evoked was numerically greater in men than women.

**ICS/LABA/LAMA**

In two RCTs [34] conducted in parallel in patients with severe symptomatic asthma and treated with the add-on long-acting muscarinic antagonist (LAMA) tiotropium (TIO) 5 μg QD to ICS plus a long-acting β₂-adrenoceptor (β₂-AR) agonist (LABA), sex did not exert an influence on the improvement in peak FEV₁, in the time to first severe asthma exacerbation, and in the time to first episode of asthma worsening vs. ICS/LABA.

**Bronchoreversibility to short acting bronchodilators**

In a recent analysis of data from the third European Community Respiratory Health Survey (ECRHS III) [36], the bronchodilator (BD) response to SALB 200 μg with regards to FEV₁/forced vital capacity (FVC) was superior in asthmatic women than in men (4.1, 95%CI 3.6–4.6 vs. 3.0, 95%CI 2.5–3.6; P < 0.01 vs. pre-BD). The BD response with respect to FEV₁ was improved in both men (4.9, 95%CI 4.1–5.8; P < 0.05 vs. pre-BD) and women (5.0, 95%CI 4.2–5.7; P < 0.05 vs. pre-BD). The increase in FEV₁ was positively associated with the fraction exhaled of nitric oxide levels after BD use in women (P < 0.05), whereas men showed no difference [36].

**Monoclonal antibodies**

Mepolizumab is an anti-interleukin-5 monoclonal antibody (mAb) approved for the treatment of severe eosinophilic asthma [63]. A recent real-world observational study of the post-marketing surveillance Australian Mepolizumab (MEPO) Registry [38] found that after treatment with mepolizumab, a greater number of women than men with severe eosinophilic asthma were classified as Asthma Control Questionnaire (ACQ) super-responders (67.0 vs. 43.0%; P < 0.01), meaning that women were more likely to achieve the best control over asthma symptoms with mepolizumab.

Omalizumab is a humanized mAb that blocks the interaction between IgE and high-affinity receptor FcεRI on inflammatory cells; it is approved for the treatment of patients with persistent severe allergic asthma, high levels of blood IgE, and at least a sensitization to a perennial allergen [63]. In a post-hoc analysis of the Patient Reported Outcomes and Xolair® In the Management of Asthma (PROXIMA) study [37], one year of treatment with omalizumab improved median ACQ scores from baseline in men (1.1 units, 95%CI 0.4–1.7; P < 0.05) and women (1.4 units, 95%CI 1.0–2.4; P < 0.05), and the asthma control rates were similar by sex. Asthma perception was worse in women than men, reaching Brief Illness Perception Questionnaire (B-IPQ) total scores of 41.8 ± 9.4 and 35.6 ± 12.0 units, respectively (P < 0.05) [37]. Sex-related differences were observed for some specific items of the B-IPQ score, with men reporting less asthma symptoms than women (4.8 ± 2.5 vs. 5.9 ± 2.4 units), less concern about the disease (4.9 ± 2.7 vs. 6.1 ± 2.8 units), lower emotional impact by the illness (4.6 ± 2.6 vs. 6.2 ± 2.7 units), and greater control by the treatment (8.7 ± 1.4 vs. 8.0 ± 2.0 units) (P < 0.05) [37]. Men had a better health status than women, reporting an EuroQoL score of 0.93 vs. 0.86 units at 12 months of therapy [37].

In a pooled analysis of data from 7 RCTs [39], treatment every 2 or 4 weeks with add-on omalizumab similarly reduced the annualized exacerbation rate in men (RR 0.67, 95%CI 0.51–0.76; P < 0.0001 vs. PCB) and women (RR 0.61, 95%CI 0.52–0.72; P < 0.0001 vs. PCB) affected by severe persistent asthma.

**Sex differences in COPD therapy**

**ICS**

According to a prospective unblinded study [40] conducted in primary care settings, women suffering from COPD who discontinued treatment with an ICS were at significantly higher risk of an adverse respiratory
outcome than men (hazard ratio [HR] 2.14, 95%CI 1.31–3.50; P < 0.01).

A post-hoc analysis of the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) [41] reported that 3 years of treatment with budesonide (BUD) 400 μg BID reduced the prevalence of phlegm symptoms (OR 0.66, 95%CI 0.52–0.83; P < 0.05 vs. PCB) in men but not in women. No change in the prevalence of wheeze, dyspnoea, and cough symptoms was detected after treatment, irrespective of sex [41].

The Inhaled Steroids Effect Evaluation in COPD (ISEEC) pooled analysis [42] of seven RCTs assessing the effectiveness of long-term ICS use in moderate to severe COPD, indicated that over the first 6 months of treatment, ICSs improved FEV₁ in both men (+42 mL) and women (+29 mL) compared to PCB (P < 0.01). In the ex-smoker group, women had a larger increase in FEV₁ with ICS therapy than did men [42]. From 6 to 36 months of therapy, both men and women from the ICS group had a similar and significant (P < 0.05) decrease in FEV₁ from baseline of -25 mL and -24 mL, respectively [42].

**Muscarinic antagonists**

In a subgroup analysis of the 4-year Understanding the Potential Long-term Impact of Tiotropium (UPLIFT) RCT [43], TIO 18 μg QD improved trough FEV₁ in both men and women (92 mL and 77 mL, respectively, P < 0.001 vs. PCB), although the annualized rates of decline in predicted FEV₁ were similar to PCB by sex. TIO reduced the risk for a first exacerbation in men (HR 0.87, 95%CI 0.81–0.93; P < 0.05) and women (HR 0.83, 95%CI 0.74–0.94; P < 0.05) compared to PCB, as well as the number of exacerbations per patient-year in men (from 0.82 ± 0.02 to 0.71 ± 0.02; P < 0.005) and in women (from 0.92 ± 0.04 to 0.77 ± 0.03; P < 0.005) [43].

| Outcomes                      | Treatments and comparisons                                                                 |
|-------------------------------|-------------------------------------------------------------------------------------------|
|                               | ICS vs. PCB or baseline                                                                   |
|                               | SABA vs. baseline                                                                         |
|                               | ICS/LABA/LAMA vs. ICS/LABA                                                                |
|                               | Omalizumab vs. PCB or baseline                                                            |
|                               | Mepolizumab vs. PCB                                                                       |
| FEV₁                           | [33]: men responded significantly better than women                                        |
|                               | [35, 36]: women ≈ men                                                                     |
| FEV₁/FVC                      | /                                                                                         |
|                               | [36]: women responded significantly better than men                                        |
| Protection against bronchial provocation | [31]: men responded significantly better than women                                     |
|                               | /                                                                                         |
| Exacerbation                  | [32]: borderline significance only in men                                                 |
|                               | [34]: women ≈ men                                                                         |
| Time to first episode of asthma worsening | [31]: men responded significantly better than women                                     |
| Asthma control                | [32]: men responded significantly better than women                                        |
| Asthma symptoms               | [32]: men responded significantly better than women                                        |
| Asthma perception             | /                                                                                         |
| Quality of life               | /                                                                                         |
| FeNO                          | /                                                                                         |
|                               | [36]: significantly greater in women than men                                             |

The greater response of a gender vs. the other one was reported when a statistically significant (P < 0.05) superiority was detected in the reference study for a specific treatment; the symbol “≈” indicates a similar, not statistically different (P ≥ 0.05) response between women and men to a specific treatment.

/: data not available, FeNO fraction exhaled nitric oxide, FEV₁ forced expiratory volume in the 1st second, FVC forced vital capacity, ICS inhaled corticosteroid, LABA long-acting β₂-adrenoceptor agonist, LAMA long-acting muscarinic antagonist, PCB placebo.

### Table 2 Evidence from the studies included in the systematic review concerning the sex-related differences in the effectiveness of asthma treatments

| Outcomes                      | Treatments and comparisons                                                                 |
|-------------------------------|-------------------------------------------------------------------------------------------|
|                               | ICS vs. PCB or baseline                                                                   |
|                               | SABA vs. baseline                                                                         |
|                               | ICS/LABA/LAMA vs. ICS/LABA                                                                |
|                               | Omalizumab vs. PCB or baseline                                                            |
|                               | Mepolizumab vs. PCB                                                                       |
| FEV₁                           | [33]: men responded significantly better than women                                        |
|                               | [35, 36]: women ≈ men                                                                     |
| FEV₁/FVC                      | /                                                                                         |
|                               | [36]: women responded significantly better than men                                        |
| Protection against bronchial provocation | [31]: men responded significantly better than women                                     |
|                               | /                                                                                         |
| Exacerbation                  | [32]: borderline significance only in men                                                 |
|                               | [34]: women ≈ men                                                                         |
| Time to first episode of asthma worsening | [31]: men responded significantly better than women                                     |
| Asthma control                | [32]: men responded significantly better than women                                        |
| Asthma symptoms               | [32]: men responded significantly better than women                                        |
| Asthma perception             | /                                                                                         |
| Quality of life               | /                                                                                         |
| FeNO                          | /                                                                                         |
|                               | [36]: significantly greater in women than men                                             |
### Table 3  Evidence from the studies included in the systematic review concerning the sex-related differences in the effectiveness of COPD treatments

| Outcomes | Treatments and comparisons |
|----------|-----------------------------|
| **FEV₁** | **Muscarinic antagonists**<br> vs. PCB or baseline | ICS vs. PCB or baseline | Discontinuation vs. baseline | **Short-acting bronchodilators** vs. LAMA | **LABA/LAMA** vs. LABA | **ICS/LABA** vs. PCB | **PDE4 inhibitor**<br> Azithromycin | **Varenicline** | **EXACT or EXACT-RS** |
| **Protection against bronchial provocation** | / | / | / | / | / | / | / | / | / |
| **Exacerbation** | [43]: women ≈ men | / | / | / | / | / | / | / | / |
| **EXACT or EXACT-RS** | [45]: significant reduction in women but not in men | / | / | / | / | / | / | / | / |
| **Adverse respiratory outcome** | / | / | [40]: men responded significantly better than women | / | / | / | / | / | / |
| Outcomes                  | Treatments and comparisons                                                                 |
|--------------------------|-------------------------------------------------------------------------------------------|
|                         | **Muscarinic antagonists**                                                                    |
|                         | vs. PCB or baseline vs. PCB or baseline Discontinuation vs. baseline vs. LAMA vs. LABA vs. ICS/LABA |
|                         | **LABA/LAMA**                                                                                 |
|                         | vs. LAMA vs. LABA vs. ICS/LABA vs. PCB vs. PCB vs. PCB vs. PCB                               |
| TDI                      | / / / / / [50]: women responded significantly better than men [51]: significant only in men |
| Symptom total score      | / / / / / [50]: women responded significantly better than men [50]: women ≈ men         |
| Phlegm symptoms          | / [41]: significant reduction in men but not in women [41]: women ≈ men                     |
| Wheeze, dyspnea, and cough symptoms | / [41]: women ≈ men                                                                         |
| Rescue medication        | / / / / [50]: numerically better in women than in men [50]: numerically better in women than in men [52]: significant only in men (numerical improvement in women) |
Table 3 (continued)

| Outcomes | Treatments and comparisons |
|----------|-----------------------------|
| Muscarinic antagonists vs. PCB or baseline | ICS vs. PCB or baseline | Discontinuation vs. baseline | Short-acting bronchodilators vs. LAMA | LABA/LAMA vs. LABA | LABA/LAMA vs. ICS/LABA | PDE4 inhibitor vs. PCB | Azithromycin vs. PCB | Varenicline vs. PCB |
| SGRQ [43], [45]: women ≈ men | / / / | / | / | / | / | / | / | / |
| Mortality [43]: significant only in men (numerical improvement in women) | / / / | / | / | / | / | / | / | / |
| Smoking cessation | / / / | / | / | / | / | / | / | / |

The greater response of a gender vs. the other one was reported when a statistically significant (P < 0.05) superiority was detected in the reference study for a specific treatment; the symbol “≈” indicates a similar, not statistically different (P ≥ 0.05) response between women and men to a specific treatment.

/: data not available, EXACT Exacerbation of Chronic Pulmonary Disease Tool, EXACT-RS EXACT-respiratory symptoms, FEV1 forced expiratory volume in the 1st second, FVC forced vital capacity, ICS inhaled corticosteroid, LABA long-acting β2-adrenoceptor agonist, LAMA long-acting muscarinic antagonist, PCB placebo, PDE4 phosphodiesterase 4, SGRQ St George’s Respiratory Questionnaire, TDI Transition Dyspnea Index.
TIO lowered the risk of all-cause mortality irrespective of sex, although the effect was significant (P < 0.05) only in men (HR 0.85, 95% CI 0.72–0.99) [43]. Total St George’s Respiratory Questionnaire (SGRQ) scores were improved with TIO in both men (between -2.3 and -3.6 units; P < 0.05 vs. PCB) and women (between -2.1 and -2.7 units; P < 0.05 vs. PCB) [43].

Li et al. [44] used data from the Lung Health Study (LHS) to investigate sex-related differences in BD response following treatment with ipratropium bromide (IB) administered at 72 μg three times a day, in mild to moderate COPD patients. After 4 months, IB improved FEV₁ from baseline by 2.94±7.53% in men and by 6.0±7.51% in women, a sex-related difference that persisted for 2 years (P < 0.05), but beyond this time point, the greater beneficial impact on FEV₁ in women was lost [44]. The BD effect of IB was found to be inversely related with body mass index (BMI), therefore women in the lowest BMI categories experienced greater benefits from therapy (P < 0.05), whereas BMI had no impact on the pharmacological response in men [44].

A pooled analysis [45] of data from moderate to severe COPD patients who participated in the GOLDEN 3 and GOLDEN 4 replicate studies found that 12 weeks of treatment with glycopyrronium bromide (GLY) 25 μg BID improved trough FEV₁ in both men (+86 mL) and women (+102 mL) (P < 0.001 vs. PCB). GLY was superior to PCB in reducing SGRQ scores in men (-3.19 units) and women (-3.58 units) (P < 0.01), with no difference by sex [45]. Although the Exacerbation of Chronic Pulmonary Disease Tool (EXACT)-respiratory symptoms (EXACT-RS) total score was reduced regardless of sex with GLY, only women achieved a significant (P < 0.01) improvement compared to PCB (-1.48 units) and to men (-2.33 units) [45]. Changes in rescue medication use were not different across treatment groups and by sex [45].

**ICS/LABA and LABA/LAMA**

In the Toward a Revolution in COPD Health (TORCH) study [46], a RCT primarily designed to determine the mortality risk from any cause over 3 years of treatment with FP/salmeterol (FP/SAL) 500/50 μg BID and its monocomponents, sex-related differences did not affect any treatment response vs. PCB. An extended analysis of the TORCH RCT [61] found that over 3 years of study, women had a numerically lower risk of mortality than men. The rate of exacerbations was higher by 25.0% (95% CI 16–34; P < 0.001) in women than in men but no difference by sex was observed in the change of SGRQ [61]. According to a post-hoc analysis of the TORCH RCT [48], the treatment effect of FP/SAL 500/50 μg BID combination or its monocomponents on the rate of FEV₁ decline was similar irrespective of sex.

In a sensitivity analysis of The TRial of Inhaled STreroids ANd long-acting β₂ agonists (TRISTAN) RCT [47], 1 year of treatment with FP/SAL 500/50 μg BID improved pre-treatment FEV₁ in both men (+127 mL, 95%CI 94–159; P < 0.05 vs. PCB) and women with COPD (+152 mL, 95%CI 95–208; P < 0.05; vs. PCB). FP/SAL reduced the rate of COPD exacerbations in men by 23.0% (95%CI 8.0–35.0; P < 0.01) and in women by 31.0% (95%CI 9.0–48.0; P < 0.01) compared to PCB; the rate of severe COPD exacerbations was decreased respectively in men by 41.0% (95%CI 25.0–53.0; P < 0.001) and in women by 36.0% (95%CI 9.0–55.0; P < 0.05) [47]. Combination therapy induced a significant (P < 0.05) improvement in SGRQ scores in men (-2.1 units, 95%CI -3.5 to -0.8) and a numerical decrease in women [47].

In a post-hoc analysis [49] of a 12-week RCT performed in moderate and severe/very severe COPD patients, combining formoterol (FOR) 12 μg BID with TIO 18 μg QD was more effective at improving the area under the curve (AUC) for FEV₁ measured 0–4 h post morning dose (FEV₁ AUC₀₋₄ h) in both men (+410 mL) and women (+320 mL) than administering TIO alone (+190 mL and +180 mL, respectively in men and women; P < 0.01). In women, the mean percentage change in FEV₁ AUC₀₋₄ h was in the range of 31.7–34.7% with FOR/TIO vs. 18.5–20.9% with TIO [49]. Men showed comparable ranges to those in women with FOR/TIO (32.9–35.7%) and TIO (15.7–19.7%) [49].

In a pooled analysis [50] of six parallel-group studies included in the IGNITE program, 26 weeks of treatment with indacaterol/GLY (IND/GLY) 100/50 μg QD improved trough FEV₁ in both men and women with moderate to very severe and severe to very severe COPD vs. FP/SAL 500/50 μg, GLY 50 μg, TIO 18 μg, and PCB (P < 0.01). Men treated with IND/GLY vs. FP/SAL or PCB experienced greater improvements in trough FEV₁ than women, while women administered IND/GLY vs. TIO had similarly higher improvements than men [50]. IND/GLY was superior to all comparators in terms of reduction in SGRQ and Transition Dyspnea Index (TDI) total scores, however it resulted more effective in women than men [50]. The use of rescue medications and symptoms total score were numerically lower in women than men after treatment with IND/GLY vs. all comparators [50].

In a pooled analysis of the Phase III ACLIFORM and AUGMENT RCTs performed in moderate to severe COPD patients [51], 24 weeks of treatment with aclindinium (ACL)/FOR 400/12 μg BID improved trough FEV₁ in both men and women (+163 mL and +101 mL, respectively; P < 0.001 vs. PCB) and post-dose FEV₁ in men and women (+334 mL and +231 mL, respectively; P < 0.001 vs. PCB). In men, ACL/FOR was superior to ACL and FOR monotherapies on trough FEV₁ (+44 mL
An analysis of a post-hoc analysis of the Effect of Indacaterol Glycopyrronium Vs Fluticasone Salmeterol on COPD Exacerbations (FLAME) RCT [52] found that in men with moderate to severe COPD, 1-year treatment with IND/GLY 110/50 μg QD was superior to FP/SAL 500/50 μg BID in reducing the annualized rates of moderate/severe exacerbations and all exacerbations (RR 0.81, 95%CI 0.73–0.91 and RR 0.88, 95%CI 0.81–0.96, respectively; P < 0.01), whereas women experienced numerically higher improvements. Compared to FP/SAL, IND/GLY increased the time to first moderate/severe exacerbation in men (HR 0.79, 95%CI 0.70–0.89; P < 0.001) and women (HR 0.76, 95%CI 0.63–0.91; P < 0.01) and the time to first all exacerbations in men (HR 0.86, 95%CI 0.79–0.94; P < 0.01) and women (HR 0.80, 95%CI 0.69–0.93; P < 0.01) [52]. The improvement in trough FEV₁ was greater with IND/GLY treatment vs. FP/SAL in both men and women (+67 mL, 95%CI 51–84 and +42 mL, 95%CI 12–71, respectively; P < 0.01) [52]. IND/GLY reduced the SGRQ total score in men by -1.3 units (95%CI -2.3 – -0.4; P < 0.01 vs. FP/SAL) and a numerical improvement was seen in women [52]. The use of rescue medications was reduced more with IND/GLY than with FP/SAL in men (-0.27 puffs/day, 95%CI -0.43 – -0.12; P < 0.001), but only numerically in women [52].

**PDE4 inhibitor**

A pooled analysis of the Roflumilast in the Prevention of COPD Exacerbations While Taking Appropriate Combination Treatment (REACT) and the Roflumilast Effect on Exacerbations in Patients on Dual Therapy (RE²SPOND) RCTs [54] documented that the phosphodiesterase (PDE4) inhibitor roflumilast 500 μg QD reduced the rate of moderate to severe exacerbations in men with COPD (RR 0.82, 95%CI 0.73–0.93; P < 0.01 vs. PCB), while women showed only a numerical decrease after 1 year of therapy.

**Bronchoreversibility to short acting bronchodilators**

The LHS of smoking patients with mild COPD [57] found that women were numerically more likely to have a 10.0% increase in post-bronchodilator FEV₁ than men undergoing methacholine bronchoprovocation test.

An analysis of data from a selected cohort of the LHS characterizing long-term changes in acute bronchodilator response to isoproterenol 200 μg over 11 years [59] found that relative and FEV₁% predicted responses were not affected by sex differences, although absolute response was greater in men than women (127.3 mL and 86.6 mL, respectively; P < 0.001).

The population-based Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) study [58] documented that acute bronchodilator reversibility to SALB was more common in women affected by COPD than in men (32.9% and 23.9%, respectively; P < 0.01).

**Antibiotics**

One year of treatment with azithromycin 250 mg QD in addition to usual inhaled therapy reduced the frequency of exacerbations in COPD patients at increased risk of exacerbations, regardless of sex (P < 0.05 vs. PCB) [55].

Han et al. [56] documented that when adjusted for relevant confounders, adding azithromycin 250 mg QD to usual care for one year improved the time to first exacerbation in both men (HR 0.72, 95%CI 0.59–0.89; P < 0.01 vs. PCB) and women (HR 0.69, 95%CI 0.55–0.87; P < 0.01 vs. PCB).

**Nicotinic acetylcholine receptor partial agonist**

In a multicentre RCT [60], mild to moderate COPD patients receiving varenicline for 12 weeks achieved a superior abstinence rate from smoking compared to PCB regardless of sex (OR 8.57, 95%CI 4.55–16.2 and OR 6.27, 95%CI 2.71–14.5, respectively in men and women; P < 0.05).

**Studies including a mixed asthma and COPD population**

A study conducted in primary care settings on a mixed population including asthmatic (10.6%) and COPD patients (3.5%) [62] found that bronchoreversibility response to SALB was numerically greater in men than women with mild obstruction, but no sex-related
differences were detected when the obstruction was moderate or severe.

**Evidence synthesis**

In asthma 44% of the evidence reported that men responded better than women to the treatments included in this systematic review, whereas this percentage was 28% in COPD. Less evidence supported a greater response of women than men to the therapy of asthma and COPD, namely in 17% and 26% respectively. Detailed information on the impact of sex on the response to the overall pharmacological treatments resulting from this systematic review in asthma and COPD is shown in Fig. 2.

Less evidence is currently available for asthma than in COPD concerning the role of sex on the efficacy of therapy, with detailed information on specific treatments and outcomes reported in Fig. 3A, B.

**Risk of bias and quality of evidence**

Of the 22 trials assessable via the Cochrane RoB 2 [31, 34, 39, 41–52, 54–57, 59–61], a low risk of bias was reported in 13 studies (59.1%) for randomization process, in 14 studies (63.6%) for deviations from intended interventions, in 19 studies (86.4%) for missing outcome data. Some studies did not report information for the risk of bias in the randomization process (9, 40.9%), deviations from intended interventions (8, 36.4%), and missing outcome data (3, 13.6%). Most the studies (20, 90.9%) had some concerns on the risk of bias for the measurement of the outcomes and a high risk of bias for the selection of the reported results. The overall risk of bias was high for most studies (20, 90.9%). Detailed information concerning the risk of bias assessment is reported in Fig. 4.

Almost all the included randomized studies were ranked as being of medium- to high-quality according to Jadad score (Table 1).

The overall quality of evidence from the observational cohort and cross-sectional studies, assessed respectively via the NOS score and JBI Checklist tool, is presented in Table 1. Two cohort studies [38, 40] were given a NOS score ≥7 and were considered of high quality, whereas four studies [33, 36, 37] were assigned a score of ≤6.

Quality assessment of cross-sectional studies indicated that one study [58] was at high risk of bias for the evaluated outcomes, another one [62] was at medium risk, and the study performed by Siroux et al. [32] was at low risk of bias.

**Discussion**

The findings resulting from this systematic review indicate that the effectiveness of therapy for asthma and COPD may be modulated by sex. When considering relevant outcomes such as lung function, exacerbation, symptoms and disease control, the current evidence is generally conflicting, although some consistent data could be found especially in asthma.

For instance, in asthmatic patients ICS was more effective in men than women in improving lung function, symptoms and disease control, and in preventing exacerbation; conversely, ICS/LABA/LAMA combination was equally effective in both men and women in improving lung function and disease control, and in reducing exacerbation. Unexpectedly, no studies are currently available on the impact of sex on ICS/LABA combination in asthma. Conflicting data are available for the effect of sex on the effectiveness of mAbs in asthmatic patients.

Regarding COPD, the current evidence is much more heterogeneous. ICS and ICS/LABA combination resulted equally effective in men and women on lung function; concerning exacerbation, PDE4 inhibitor was more effective in men than women, whereas azithromycin was equally effective in both sexes; no sex-related difference was detected for muscarinic antagonists on disease control. Considering the dual bronchodilation therapy, men responded better than women when LABA/LAMA was compared to ICS/LABA against the risk of exacerbation, whereas no sex-related influence was detected vs. LAMA and LABA. Dyspnea improved more in women than in men when comparing LABA/LAMA vs. ICS/LABA and LAMA, but not vs. LABA. Inconsistent data are available for the impact of sex on the effect of LABA/LAMA vs. ICS/LABA and LAMA on lung function. Surprisingly, no studies have been performed to assess the sex-related response to ICS/LABA/LAMA in COPD.

Several studies have investigated the role of sex on receptor expression in human airways and murine models of chronic obstructive respiratory disorders. As expected, the main evidence was raised from research on sex-steroids that activate estrogen receptors (ER) or androgen receptors (AR).

AR signalling induced by androgens stabilizes CD4+ regulatory T cells (Tregs) suppressive function, providing a mechanism for higher prevalence of asthma in women compared with men [64]. This evidence is supported by the fact that the higher airway expression of AR and higher androgen levels in men are associated with better lung function, fewer symptoms, and a lower fraction exhaled nitric oxide (FeNO) in asthma [65]. Furthermore, the activation of AR may exert beneficial effect in asthma by ameliorating airway hyperresponsiveness (AHR) and type 2 inflammation via reducing intracellular calcium influx and modulating complex mechanisms such as the interleukin (IL) 17A pathway [66–68].

Concerning estrogens, they mainly act by activating both the ER forms, with ER-α having detrimental effect
in the airways and ER-β being characterized by protective activity against AHR and remodelling. These beneficial effects are mediated by the reduction of intracellular calcium, suppression of nuclear factor kappa B (NF-κB) pathway, and modulation of platelet-derived growth factor (PDGF) inducing airway smooth muscle (ASM) proliferation [69–73]. The variations in ERα and ERβ expression profile on ASM during inflammation may contribute to estrogen signaling in asthma [74]. In addition, estrogens may enhance the IL-4–induced M2 gene expression in alveolar macrophages and those derived from bone marrow [75]. Thus, an imbalance in the expression or activity of ERα and ERβ may be linked to the severity of disease in women.

Also other sex hormones, such as progesterone (P4), may have a role in asthma by altering the function of a key component of the mucociliary apparatus [76]. Furthermore, while normal women have cyclical changes in the function and density of β2-AR in the luteal phase during the premenstrual period, in asthmatic patients a loss of the normal cyclical pattern in β2-AR regulation has been detected, a condition related to AHR during bronchoprovocation test [77].

Sex hormones may modulate also the expression of muscarinic acetylcholine receptors (mAChR). The activation of ER-α is related to altered expression of M2 mAChR, leading to increased AHR [78]. Moreover, in women with COPD the lungs have a greater gene expression for the M3 mAChR relative to M2 mAChR than in male [44]. Of note, the extent of bronchorelaxant response is related with BMI, such that a larger improvement in lung function elicited by muscarinic antagonists has been reported in thin women [44].

Indeed, COPD is characterized by high sex-dependent T-cell profile. In this regard, a greater expression of chemokine receptor CCR5 on CD8+ T cells and higher amount of CXCR3+CD8+ T cells was detected in bronchoalveolar lavage (BAL) or blood in women smokers with COPD compared to those without COPD. Moreover, across these patients the Th1/Tc1 immune response was related to macrophage count in BAL and goblet cell density, and the extent of emphysema was associated to the Th2/Tc2 response [44]. Conversely, the expression of CCR5 on CD4+ and CD8+ T cells was lower in BAL from male smokers with COPD compared to subjects without COPD [79]. Overall, this evidence supports different
Fig. 3 Response to pharmacological treatments in asthma A and COPD B according to specific outcomes and number of evidences as resulting from the studies included in the systematic review. The greater response of a gender vs. the other one was reported when a statistically significant (P < 0.05) superiority was detected for a specific treatment. COPD chronic obstructive pulmonary disease, FeNO exhaled nitric oxide, ICS inhaled corticosteroids, LABA long-acting β2-adrenoceptor agonist, LAMA long-acting muscarinic antagonist, PDE4 phosphodiesterase 4, SABA short-acting β2-adrenoceptor agonist
Fig. 4 Traffic light plot for the assessment of the risk of bias of each included randomized trial A and weighted plot for the assessment of the overall risk of bias B via the Cochrane RoB 2 tool (B) (n = 22 studies). Traffic light plot reports five risk of bias domains: D1, bias arising from the randomization process; D2, bias due to deviations from intended intervention; D3, bias due to missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of the reported result; green circle represents low risk of bias, yellow circle indicates some concerns on the risk of bias, red circle reports high risk of bias, and blue circle indicates insufficient information on the risk of bias. RoB risk of bias.
links between cellular events, inflammation, and clinical manifestations of COPD in women compared to men.

Most of the pre-clinical evidence regarding the influence of sex on the expression of receptors in the airways originate from murine models of AHR that, unfortunately, may have just a relative translational impact on the pharmacotherapy in asthma and COPD. Moreover, across the records included in this systematic review, only 2 RCTs were specifically designed to assess the influence of sex on the effectiveness of treatment in asthma [31] and COPD [57]. The remaining papers reported data from trials or post-hoc analyses of previous studies for which the assessment of sex on asthma and COPD therapy was not even a pre-specified endpoint, leading to high risk of Type I error, or observational trials that were characterized by major intrinsic limitations. Another limitation of this systematic review is related to the unbalanced number of males and females enrolled in the studies, especially in COPD: almost all the trials had a higher number of males than females. Thus, the high risk of bias resulting from the Cochrane RoB 2 tool was extensively expected, suggesting that the provided evidence should be interpreted with caution.

Conclusions

Indeed, the findings of this systematic review highlight that the number of studies in asthma and COPD looking at the same drug and outcome is currently small, making difficult to draw solid conclusions. However it seems that, as supported also by pre-clinical findings, ICS may be generally less effective in women than in men to treat asthma. Consistent evidence also suggests that in asthmatic patients ICS/LABA/LAMA combination may be equally effective in both men and women. Overall, excluding the effort of independent research, Big Pharma has demonstrated scarce interest in assessing the potential different impact of sex on the pharmacological response to asthma and COPD therapy. In this regard, this systematic review highlights the strong pharmaceutical and clinical need of adequately investigating this issue that to date remains very controversial. A first step to manage this important and discriminatory scientific lack could be to make the data from large investigational clinical trials in asthma and COPD available specifically for each sex rather than as overall results. Moreover, considering that clinical trials in asthma and COPD are characterized by imbalanced enrollment ratio between men and women leading to possible sex bias in measured outcomes [9, 80], it is expected that the randomization procedures of future RCTs will be set to equally enroll both sexes. Finally, but not less important, pre-specified analyses in men and women should be planned in the trial protocols, a necessary condition that should be requested also by the regulatory agencies.

Abbreviations

ACQ: Asthma Control Questionnaire; AHR: Airway hyperresponsiveness; ASM: Airway smooth muscle; AR: Androgen receptor; AUC: Area under the curve; β2-AR: β2-Adrenoceptor; BAL: Bronchoalveolar lavage; BD: Bronchodilator; BID: Twice daily; B-IPQ: Brief Illness Perception Questionnaire; BMI: Body mass index; CENTRAL: Cochrane Central Register of Controlled Trials; COPD: Chronic obstructive pulmonary disease; DECIMAL: Data extraction for complex meta-analysis; ER: Estrogen receptor; EXACT: Exacerbation of Chronic Pulmonary Disease Tool; EXACT-RS: EXACT-respiratory symptoms; FDA: Food and Drug Administration; FeNO: Fraction exhaling nitric oxide; FEV1: Forced expiratory volume in the 1st second; FEV1/FVC, measured 0–4 h post morning dose; FOR: Formoterol; FP: Fluticasone propionate; G1: Glycophorin; HR: Hazard ratio; I: Ipratropium bromide; ICS: Inhaled corticosteroid; IL: Interleukin; IND: Indacaterol; JBI: Joanna Briggs Institute; LABA: Long-acting β2-AR agonist; LAMA: Long-acting muscarinic antagonist; mAChR: Muscarinic acetylcholine receptor; NCD: Non-communicable disease; NF-κB: Nuclear factor kappa B; NOS: Newcastle–Ottawa Scale; OCS: Oral corticosteroid; OR: Odds ratio; PCB: Placebo; PD: Pharmacodynamics; PDE4: Phosphodiesterase 4; PGF2α: Platelet-derived growth factor; PD20: Provocative dose of methacholine causing a 20% fall in FEV1; QD: Once daily; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols; RCT: Randomized controlled trial; RoB 2: Risk of Bias 2; RR: Relative rate; SALB: Salbutamol; SAL: Salmeterol; SGRQ: St George's Respiratory Questionnaire; Tregs: Regulatory T cells; TDI: Transition Dyspnea Index; TIO: Tiotropium.

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Author contributions

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