

# ***Evidence Synthesis***

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## **Number 215**

### **Screening for Chronic Obstructive Pulmonary Disease: A Targeted Evidence Update for the U.S. Preventive Services Task Force**

**Prepared for:**

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5600 Fishers Lane  
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**Prepared by:**

Kaiser Permanente Research Affiliates Evidence-based Practice Center  
Kaiser Permanente Center for Health Research  
Portland, OR

**Investigators:**

Jennifer S. Lin, MD, MCR  
Elizabeth M. Webber, MS  
Rachel G. Thomas, MPH

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## Structured Abstract

**Objective:** We conducted a targeted evidence update to support the US Preventive Services Task Force in updating its 2016 recommendation on Screening for Chronic Obstructive Pulmonary Disease (COPD). Our review addressed three key questions: 1) Does screening for COPD improve health-related quality of life or reduce morbidity or mortality?, 2) Does treatment of screen-detected or mild to moderate COPD improve health-related quality of life or reduce morbidity or mortality?, 3) What are the adverse effects of COPD treatments in this population?; and one contextual question: 1) Does identifying asymptomatic adults with COPD improve the delivery and uptake of targeted preventive services (e.g., smoking cessation, recommended immunizations, lung cancer screening)?

**Data Sources:** We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and CINAHL from January 1, 2015, to January 22, 2021, to identify literature published since the previous recommendation. Because the previous review did not include non-pharmacologic interventions, we supplemented these searches by examining reference lists of relevant recent reviews to identify studies prior to 2015.

**Study Selection:** Two investigators independently reviewed abstracts and full-text articles against a set of *a priori* inclusion and quality criteria. Inclusion criteria for treatment benefits and harms specified persons with mild (defined as forced expiratory volume in 1 second [FEV<sub>1</sub>] ≥ 80 percent predicted) to moderate (FEV<sub>1</sub> 50-79 percent predicted) COPD or a mean population FEV<sub>1</sub> ≥ 60 percent predicted.

**Data Analysis:** One investigator abstracted data into an evidence table and a second investigator checked these data. We provide a narrative synthesis of the newly identified evidence for each question; quantitative synthesis was not appropriate due to heterogeneity and few trials for any given intervention and outcome.

**Results:** We found no trials examining the effectiveness of screening or active case finding for COPD on health outcomes. We included 16 trials evaluating the treatment of mild to moderate, or minimally symptomatic, COPD: 3 trials (n=20,058) evaluated long acting beta agonists (LABA), long acting muscarinic antagonists (LAMA), and/or inhaled corticosteroids (ICS), and 13 trials (n=3,657) evaluated non-pharmacologic interventions (i.e., self-management interventions, exercise counseling interventions, supervised exercise and pulmonary rehabilitation interventions, and clinician education interventions). Two trials (SUMMIT and UPLIFT) found that LABA, LAMA, ICS, or LABA/ICS reduced exacerbations or clinically important deterioration in persons with fairly symptomatic moderate COPD. One trial (UPLIFT) found that LAMA, specifically tiotropium, also reduced exacerbations in a subgroup analysis (n=357) of persons with minimal symptoms (i.e., GOLD category A). Overall, there was no consistent benefit observed for any type of non-pharmacologic intervention across a range of patient outcomes. One of the two trials (n=114) evaluating the same exercise-focused web-based intervention in a VA population demonstrated a reduction in COPD exacerbations at 65 weeks. Other trials, not conducted in the US, evaluating more intensive self-management interventions, supervised exercise, and pulmonary rehabilitation interventions in persons with mild to moderate COPD, or minimal symptoms, did not demonstrate a reduction in exacerbations or other

outcomes. Only three included trials reported on smoking cessation, vaccination, or lung cancer screening outcomes. These trials, combined with six additional comparative studies evaluating the incremental value of receipt of spirometry on smoking cessation, found no consistent improvement in smoking cessation. Only one trial evaluating a clinician training intervention to improve COPD care reported vaccination outcomes and demonstrated an improvement in uptake of influenza vaccination. None of the included treatment trials that reported adverse effects found significant harms. Two large observational studies in a screen-relevant population demonstrated an association of the initiation of LAMA or LABA with the risk of a serious cardiovascular event in treatment-naïve patients and an association of ICS use with the risk of developing diabetes.

**Limitations:** It is unclear how generalizable the observed treatment benefit, the reduction of exacerbations, is to a screen-detected population, as these findings were primarily in persons with fairly symptomatic moderate COPD. It is unclear if and how small sample sizes, usual care comparators in trials conducted outside the US, and/or poor adherence to the non-pharmacologic interventions contributed to the largely null findings of these trials. The small number of included participants and limited length of followup in the majority of included trials (or their relevant subgroup analyses) limits the ability to detect uncommon harms or longer-term harms. Harms of LABA, LAMA, and ICS demonstrated in the included observational trials should be interpreted in context of the larger body of literature on harms of inhaled therapies.

**Conclusions:** The findings of this targeted evidence update are generally consistent with the findings of the previous systematic review supporting the 2016 recommendation. To date, there are still no comparative studies on the effectiveness of screening or active case finding for COPD on patient health outcomes. The demonstrated benefits of pharmacologic treatment for COPD are still largely limited to persons with moderate airflow obstruction; and there was no consistent benefit observed for a range of non-pharmacologic interventions in mild to moderate COPD, or in minimally symptomatic persons with COPD.

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# Chapter 1. Introduction

## Purpose

The Agency for Healthcare Research and Quality (AHRQ) has requested a targeted evidence update focused on screening for and treatment of chronic obstructive pulmonary disease (COPD). This topic was last reviewed in 2016,<sup>1</sup> at which time the United States Preventive Services Task Force (USPSTF) reissued a D recommendation against routine screening for COPD in asymptomatic adults (i.e., individuals who do not recognize or report respiratory symptoms).<sup>2</sup> This targeted update will be used by the USPSTF to update its 2016 recommendation using the reaffirmation process.<sup>3</sup>

## Condition Background

### Condition Definition

Chronic obstructive pulmonary disease (COPD) is defined by a reduction in airflow that is not entirely reversible. Both current guidelines and the community standard for diagnostic spirometry in the United States require that fixed obstructive physiology be identified by a post-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) less than 0.70.<sup>4</sup> COPD is a progressive, chronic condition without a known cure. COPD is characterized by continual respiratory decline often associated with acute exacerbations that can result in hospitalization and ultimately death.<sup>4-6</sup> Although the degree of obstruction and symptoms (e.g., dyspnea, cough, fatigue) progress over time, the trajectory of decline can vary significantly among patients due to the complex interaction of genes with environmental exposures and other risk factors.<sup>7, 8</sup>

COPD can be classified by the degree of obstruction, or symptoms, or both (**Table 1**). The degree of obstruction characterized by the post-bronchodilator FEV<sub>1</sub> percent predicted (i.e., ratio of volume exhaled in the first second over the volume predicted by any of a number of reference equations based on age, gender, race, and height).<sup>4, 9</sup> In addition to the severity of airflow limitation (i.e., spirometric grade), the 2022 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management and Prevention of COPD also recommends patients undergo assessment of their symptoms using standardized assessment tools (i.e., Modified British Medical Research Council [mMRC] questionnaire or COPD Assessment Test [CAT]).<sup>10</sup> The mMRC is a dyspnea scale and the CAT captures a wider range of symptoms (e.g., cough, phlegm production, chest tightness, exercise tolerance, energy).

### Prevalence and Risk Factors

In 2020, the Centers for Disease Control and Prevention (CDC) reported that chronic lower respiratory disease, composed chiefly of COPD, was the sixth leading cause of death in the United States, in spite of COPD-related mortality declining over the past 20 years.<sup>11, 12</sup> The prevalence of COPD in U.S. adults varies from approximately 5 to 20 percent, depending on the

populations studied and the disease criteria used. Measurements of the prevalence and burden of COPD are variable because prevalence estimates rely on a mix of self-report, spirometry, and administrative sources. Estimates from the 2020 Behavioral Risk Factor Surveillance System (BRFSS) showed that 6.2 percent of adults reported having been diagnosed with COPD.<sup>13</sup> A 2019 systematic review estimated that the prevalence of all stages of COPD in the Americas was 14.5 percent.<sup>14</sup>

The major risk factor for developing COPD and COPD mortality is exposure to smoke or fumes, notably direct or indirect exposure to cigarette smoke.<sup>15</sup> In 2017, the age-adjusted prevalence of COPD was 15.2 percent among current smokers, 7.6 percent among former smokers, and 2.8 percent among adults who had never smoked based on BRFSS estimates.<sup>16</sup> Certain occupations, such as mining, farming and industrial work, which expose individuals to various inflammatory agents and irritants (e.g., respiratory crystalline silica, coal mine dust, toxins, organic dust, industrial chemicals), have been associated with the development of COPD.<sup>17, 18</sup> Occupational exposures are estimated to contribute to 15 percent of COPD cases. The most common environmental exposures linked to COPD include traffic pollutants and wood smoke.<sup>19</sup> Additionally, exposure to secondhand smoke, heredity, a history of childhood respiratory infections, and asthma have been shown to increase the risk of developing the disease.<sup>15, 19-23</sup> The higher prevalence of and morbidity from COPD in persons of low socioeconomic status (SES) is due to difference in health behaviors, sociopolitical factors, as well as social and structural environmental exposures.<sup>24</sup> And the higher prevalence of and morbidity from COPD in rural as compared to urban areas in the United States is, in part, related to SES (i.e., rural residents poorer and less education), as well as greater obstacles to care.<sup>25</sup>

COPD prevalence also appears to vary by sex and racial and/or ethnic groups. Although prevalence and mortality are higher in men than women, the trend over time suggests more improvement for men than women. Data from the National Vital Statistics System (NVSS) found that age-adjusted COPD-related mortality for men declined from 57 deaths per 100,000 in 1999 to 40.5 in 2019; however, for women age-adjusted COPD-related mortality remained relatively stable, 35.3 deaths per 100,000 in 1999 and 34.3 in 2019.<sup>12</sup> This is thought to be due to a variety of factors, including increasing smoking rates among women, differences in environmental exposures, and potential biological or hormonal mechanisms affecting the susceptibility to COPD.<sup>26</sup> Data from the 2017 BRFSS found the highest rates of COPD were among Native American/Alaska Native populations (11.9%) followed by those identified as ‘other/multiracial’ (9.3%), White (6.7%), Black (6.6%), ‘Hispanic’ (3.6%), Native Hawaiian/Pacific Islander (3.3%), and Asian (1.7%).<sup>16</sup> Analysis of data from BRFSS indicates that disproportionate socioeconomic challenges account for the comparatively high prevalence among Native American/Alaska Native populations.<sup>27</sup> Native Americans also have the highest prevalence of current smoking that most other racial and/or ethnic group in the United States. In 2019, 20.9 percent of Native American/Alaska Native adults in the United States smoked cigarettes compared with 14.0 percent of US adults overall.<sup>28</sup> According to 2018 data from the NVSS, age-adjusted death rates per 100,000 persons for chronic lower respiratory disease (mostly COPD) was highest in White adults (45.0), followed by Native American/Alaska Native adults (36.4), then Black (30.5), ‘Hispanic or Latino’ (17.0) and Asian/Pacific Islander (11.6) adults.<sup>29</sup> And although White adults have a higher prevalence of COPD than Black adults, Black adults



experience higher hospitalizations rates, worse COPD-related quality of life, and their COPD-related mortality is not declining at the same rate as White adults.<sup>30</sup>

## Screening and Active Case Finding

Many patients with COPD go undetected despite having symptoms for multiple reasons, including under-recognition and/or under-reporting of mild symptoms (e.g., dyspnea) or nonspecific symptoms (e.g., fatigue). Therefore, screening or active case finding (i.e., systematically assessing for symptoms and/or risk factors and performing spirometry) would detect persons otherwise not diagnosed with opportunistic case finding as part of routine care. Earlier diagnosis of COPD may help prevent poorer outcomes and higher economic costs typically associated with persons diagnosed at more advanced stages.<sup>31-33</sup> Earlier COPD diagnosis may result in better disease management with non-pharmacologic interventions (e.g., smoking cessation, exercise) and medications to reduce dyspnea, exacerbations, and to improve quality of life. Overall, adults with yet undiagnosed COPD generally have fewer symptoms and/or better lung function than their diagnosed counterparts.<sup>34, 35</sup> One recent and large prospective Danish cohort study examined the rates of undiagnosed COPD in individuals considered at risk for COPD (defined as age 40 years or older, with cumulative tobacco consumption of ten years or greater). Eleven percent of at-risk participants met the COPD criteria, 78 percent of whom were yet undiagnosed.<sup>36</sup> Of those who were yet undiagnosed, 89 percent had mild to moderate COPD and 71 percent of were symptomatic. However, most of those who were symptomatic yet undiagnosed, had minimal symptoms, 73 percent had an mMRC score of less than 2. Adults with asymptomatic undiagnosed COPD had a mean FEV<sub>1</sub> of around 71 percent predicted, compared with an FEV<sub>1</sub> of around 66 percent predicted in persons with symptoms, yet undiagnosed. All adults with undiagnosed COPD had an increased risk of exacerbations and pneumonia, including those who were asymptomatic.<sup>36</sup> Other studies have demonstrated that screening or active case finding typically identifies persons with mild to moderate COPD or mean population FEV<sub>1</sub> ≥ 60 percent.<sup>37-39</sup>

Screening or active case finding for COPD in primary care may involve screening those at risk (e.g., based on age and smoking status) for COPD using spirometry or using screening questionnaires for more detailed risk and symptoms assessment to inform who receives spirometry. These questionnaires can typically be quickly administered or self-administered (e.g., the Lung Function Questionnaire [LFQ],<sup>40, 41</sup> the COPD Diagnostic Questionnaire [CDQ],<sup>42, 43</sup> the COPD population screener [COPD-PS],<sup>44</sup> and the Salzburg COPD-screening questionnaire [SCSQ]).<sup>45</sup> Other brief screening questionnaires can incorporate peak expiratory flow (PEF) (e.g., COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk [CAPTURE TM]).<sup>46, 47</sup> Other ‘pre-screener’ can include point of care tools measuring FEV known as ‘handheld spirometry’ (e.g., COPD-6 device [Vitalograph Ltd, Ireland]).<sup>48</sup> Screening spirometry, either preceded by risk assessment or not, is administered without medication (i.e., pre-bronchodilator spirometry).<sup>4</sup> Since the diagnosis of COPD requires persistent airway obstruction, all abnormal screening spirometry should be followed up with spirometry testing following the administration of an inhaled medication like albuterol (i.e., post-bronchodilator spirometry).<sup>4, 9</sup> This step can be done with screening or in a separate step depending on the setting, training of staff, and equipment available. The previous systematic review found evidence to suggest that externally validated questionnaires (i.e., COPD Diagnostic

Questionnaire [CDQ]) had adequate test performance for the detection of COPD and more limited evidence to demonstrate that spirometry (both screening and post-bronchodilator) could identify COPD.<sup>1</sup>

## Treatment Approaches

The management and treatment of mild to moderate or minimally symptomatic COPD includes both pharmacologic and non-pharmacologic interventions. Smoking cessation is by far the most important secondary prevention intervention for individuals with COPD because combustible cigarette smoking accelerates the deterioration of lung function in patients with the disease.<sup>4, 49</sup> The Lung Health Study demonstrated that smoking cessation counseling in adults with mostly asymptomatic mild to moderate COPD reduced all-cause mortality.<sup>50, 51</sup> In addition to smoking cessation, many non-pharmacologic interventions address self-management of disease, diet, exercise, and uptake of recommended preventive services like influenza and pneumococcal immunizations. Although pulmonary rehabilitation has been evaluated in persons with low symptom burden, in the United States it is currently used for COPD patients who remain symptomatic, despite optimal pharmacological therapy. Pharmacologic management of mild to moderate COPD primarily treats symptoms and may improve functioning and quality of life but does not appear to prevent the progression of disease. Medications used in the management of COPD include bronchodilators and anti-inflammatory therapies. The mainstay of pharmacologic treatment of mild to moderate COPD is bronchodilators, i.e., short acting beta-agonists (SABA), long-acting beta-agonists (LABA), short-acting muscarinic antagonists (SAMA), and long-acting muscarinic antagonists (LAMA).<sup>52</sup> Typically short-acting bronchodilators are used in those with the least symptom burden, then long-acting bronchodilators in those who are more symptomatic, and combination LABA/LAMA in those with high initial symptom burden or history of exacerbations. The addition of inhaled corticosteroids (ICS) is generally used in persons with high symptom burden, co-existing asthma, and/or eosinophilia.

## Current Clinical Practice and Recommendations of Others

Major clinical practice guidelines recommend against routine general screening for COPD in asymptomatic patients; however, they do recommend case finding in patients presenting with respiratory symptoms associated with the disease (e.g., dyspnea, chronic cough, sputum production). GOLD recommends active case finding in patients with symptoms and/or risk factors (**Table 2**).

Generally, screening for COPD using pre-bronchodilator spirometry is not widely used in primary care practice in the United States. Additionally, data suggests that using spirometry for case finding in a manner consistent with guideline recommendations is vastly underutilized.<sup>30, 53</sup> This underutilization may be due to a number of causes, including but not limited to low diagnostic yield and complexity of the testing.<sup>38, 54-60</sup> In the NHANES III, 63.3 percent of adults who were found to have airflow obstruction reported never having received a previous diagnosis of COPD.<sup>21</sup> In one US study, COPD Genetic Epidemiology (COPDGene), Black adults had a higher odds of not having a prior COPD diagnosis regardless of severity of airflow obstruction compared to White adults (44 percent versus 29 percent undiagnosed, respectively).<sup>61</sup> And

women were more than three times as likely than men to have severe disease at the time of diagnosis.<sup>62</sup>

## Previous USPSTF Recommendation

In 2016 the USPSTF issued a D Recommendation against screening for COPD in asymptomatic adults (defined as individuals who do not recognize or report respiratory symptoms).<sup>2</sup> Previously the USPSTF did not find direct evidence that screening for COPD in asymptomatic persons improved health-related quality of life (HRQoL), morbidity, or mortality. Although they found that screening for COPD could accurately identify persons with COPD, they determined that, based on the included evidence, early detection of COPD did not alter the course of the disease or improve patient outcomes. The previous systematic review found no treatment studies conducted in patients with screen-detected COPD and relatively few in patients with mild COPD.<sup>1</sup> Overall, the included treatment evidence was largely limited to subgroup analyses, almost exclusively among individuals with moderate COPD, and primarily the more severe end of moderate COPD (e.g., FEV<sub>1</sub> 60 percent predicted). Even among these groups, the only consistent benefit observed was reduced COPD exacerbations with no consistent benefits in mortality, dyspnea, or HRQoL. The USPSTF did not judge this evidence to be widely applicable to persons with COPD identified through screening.

This review also found limited evidence that did not support screening as a means to improve smoking cessation rates or the uptake of other recommended preventive services.<sup>1</sup> In addition, the USPSTF also judged that the amount of time and effort required to screen for COPD in asymptomatic persons (using screening spirometry with or without prescreening questionnaires) was not trivial. Therefore, based on the moderate certainty of no net benefit and opportunity cost of screening asymptomatic adults, the USPSTF renewed their 2008 D recommendation. However, in this recommendation statement, the USPSTF included language encouraging clinicians to offer smoking cessation interventions to all patients who currently smoke and to pursue case finding for COPD in patients with risk factors (e.g., exposure to cigarette smoke or heating fuels, occupational exposure to dusts or chemicals, family history of  $\alpha$ 1-antitrypsin deficiency).

## Chapter 2. Methods

### Scope

Given that the prior USPSTF D recommendation was primarily based on the lack of evidence for early treatment of COPD, or treatment in persons with un- or under-recognized symptoms, and not the ability of screening to detect persons with COPD, this targeted update focuses on three key questions to address the important evidence gaps from the prior review. Consistent with the prior review and the primary research, this review focuses on adults age 40 or older given the distribution of COPD in adults. This review newly includes a synthesis of non-pharmacologic interventions, in addition to pharmacologic therapies, in screen-detected or screen-relevant adults with COPD.

### Key Questions and Analytic Framework

In consultation with members of the USPSTF, we developed an analytic framework (**Figure 1**) and three Key Questions (KQs) to guide our targeted evidence update.

#### KQs

1. Does screening for COPD improve health-related quality of life or reduce morbidity or mortality?
2. Does treatment of screen-detected or mild to moderate COPD improve health-related quality of life or reduce morbidity or mortality?
3. What are the adverse effects of COPD treatments in this population?

In addition to these KQs, we also addressed if identifying asymptomatic adults with COPD improves the delivery and uptake of targeted preventive services (e.g., smoking cessation, recommended immunizations, lung cancer screening)?

### Data Sources and Searches

We conducted a literature search of MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL from January 1, 2015, to January 22, 2021, to identify literature published since the previous review for the USPSTF. We worked with a research librarian to develop our search strategy (**Appendix A**). Because the previous review did not include non-pharmacologic interventions, we supplemented these searches by examining reference lists of recent reviews and primary studies, and citations provided by experts, to identify major studies prior to 2015. We limited our searches to articles published in English and managed search results using Endnote® version X7 (Thomson Reuters, New York, NY).

## Study Selection

We developed specific inclusion criteria to guide study selection (**Appendix A Table 1**). Two reviewers independently reviewed the title and abstracts of all identified articles using DistillerSR (Evidence Partners, Ottawa, Canada). Two reviewers then independently evaluated the full text of all potentially relevant articles, with differences reviewed by discussion.

To address KQ1 on the effectiveness of screening or risk tailored screening (referred to as active case finding) for COPD on health outcomes, we included randomized controlled trials (RCTs) of any screening method (e.g., spirometry, questionnaire or risk assessment followed by spirometry) in asymptomatic adults, adults who have symptoms that are undetected by the patient or clinician (e.g., mild dyspnea that goes unnoticed), or adults who have nonspecific symptoms (e.g., sporadic sputum production or cough, fatigue) that have gone unreported or unrecognized as related to COPD. We excluded studies conducting surveillance for COPD in populations at very high risk for COPD, i.e., persons with alpha-1 antitrypsin deficiency and workers with known occupational exposures.

To address KQ2 and 3 on the benefits and harms of treatment, we focused on studies that were conducted in persons with screen-detected COPD or screen-relevant patients, meaning adults with mild to moderate COPD by spirometry (or a mean population FEV<sub>1</sub> ≥ 60 percent predicted) and/or low symptom burden as defined by GOLD criteria. Pharmacologic therapies included inhaled bronchodilators (i.e., SABA, SAMA, LABA, LAMA), ICS, or combinations of these treatments. Non-pharmacologic therapies included self-management interventions, case management, behavioral counseling, exercise therapy, and pulmonary rehabilitation. We also included clinician training and education interventions if studies reported patient outcomes. We excluded interventions that are primarily used in persons with more severe or symptomatic disease (e.g., oxygen therapy, oral corticosteroids, phosphodiesterase-4 inhibitors, antibiotics, surgical therapies). Study designs were limited to randomized or non-randomized trials and for harms (KQ3) and large registry studies of drug safety. Treatment trials had to include a minimum of 6 months followup.

## Quality Assessment and Data Abstraction

Two reviewers independently assessed the methodologic quality (risk of bias) of each included study using predefined criteria (**Appendix A Table 2**). We assigned each study a quality rating of “good,” “fair,” or “poor” according to the USPSTF’s study design-specific criteria.<sup>3</sup> We supplemented these criteria with modified questions from the Newcastle-Ottawa Scale for nonrandomized studies of harms.<sup>63</sup> Disagreements were resolved by discussion. One investigator abstracted data into an evidence table and a second investigator checked the accuracy of the abstracted data against the article. We abstracted details on the study’s design, patient characteristics, intervention and comparator characteristics, as well as outcomes specified in the inclusion criteria. Outcomes of interest included mortality, morbidity from COPD, HRQoL, and serious harms as defined by study author or adverse events requiring unexpected medical attention and/or resulting in death. COPD morbidity included objective physical performance measures like the 6-minute walk test (6MWT). Quality of life measures included externally

validated generic measures like the Short Form (36) Health Survey (SF-36) or EuroQual (EQ-5D), as well as disease-specific measures like the St. George's Respiratory Questionnaire (SGRQ), and the COPD Assessment Test (CAT). The SGRQ score can range from 0 to 100, with higher scores indicating more limitations on overall health, daily life, and perceived well-being.<sup>64</sup> The CAT score can range from 0 to 40, with higher scores representing worse quality of life.<sup>65</sup> When reported, we also abstracted dyspnea symptom scores and mental well-being outcomes as these were conceptualized as part of HRQoL. Physiologic outcomes of change in FEV<sub>1</sub> were not abstracted.

## **Data Synthesis and Analysis**

This targeted update synthesized the evidence published since the USPSTF last considered this topic in 2016. Therefore, the narrative synthesis does not include older evidence previously considered by the USPSTF. Given the limited number of pharmacologic trials and clinical heterogeneity in the non-pharmacologic trials, we did not conduct any quantitative synthesis. To understand the totality of the evidence for these key questions, we included a summary table comparing the findings of the interval evidence (included in this review) to the previous review supporting the 2016 recommendation.

## **Expert Review and Public Comment**

The draft Research Plan was posted for public comment on the USPSTF website from July 2 to July 29, 2020. The USPSTF received comments regarding clarification of the scope of the targeted evidence update (as part of the reaffirmation process), particularly regarding the included populations and interventions. In response, the Research Plan was modified to clarify that “asymptomatic” includes persons with yet undetected signs or symptoms of COPD. In addition, text was added to specify that the included population for the KQs related to treatment are persons with mild to moderate COPD, populations with a minimum mean FEV<sub>1</sub> of 60 percent predicted, or both. Last, the uptake of lung cancer screening was added to smoking cessation and recommended immunizations as a preventive service for the Contextual Question. A final research plan was posted on the USPSTF's Web site on October 8, 2020.

A prior version of this report was reviewed by three content experts and invited representatives of Federal partners. All reviewer comments and their disposition were presented to the USPSTF and revisions in response to comments are reflected in this report. Additionally, a draft of this report was posted November 2nd to December 6th, 2021 for public comment on the USPSTF website along with the accompanying USPSTF draft recommendation statement. Minor edits for clarity and updated citations were added based on public comment.

## **USPSTF and AHRQ Involvement**

The authors consulted with USPSTF members during the development of the research plan, including the analytic framework, KQs, and inclusion criteria. An AHRQ Medical Officer

provided project oversight, reviewed the draft and final versions of the evidence update, and assisted with public comment on the research plan and draft report. The USPSTF and AHRQ had no role in the study selection, quality assessment, or writing of the evidence update.

# Chapter 3. Results

## Literature Search

Results of this search represent literature published since the previous systematic review on this topic. We screened 6387 abstracts and assessed 229 full-text articles for inclusion (**Appendix B Figure 1**). After screening the full-text articles, no studies were included for KQ1, 16 studies (in 28 articles)<sup>66-80</sup> were included for KQ2, and eight studies (in 20 articles) for KQ3.<sup>69, 72, 75, 76, 78, 81, 82</sup> The full list of included studies and their ancillary articles is available in **Appendix C**. The list of excluded studies with reasons for their exclusion is available in **Appendix D**.

### **KQ1. Does Screening for COPD Improve Health-Related Quality of Life or Reduce Morbidity or Mortality?**

#### **Summary of Results**

We found no trials examining the effectiveness of screening or active case finding for COPD on health outcomes. Screening or active case-finding studies to date are limited to describing the yield of COPD cases (Chapter 4: Discussion).

### **KQ2. Does Treatment of Screen Detected or Mild to Moderate COPD Improve Health-Related Quality of Life or Reduce Morbidity or Mortality?**

#### **Summary of Results**

We included 16 trials evaluating the treatment of mild to moderate, or minimally symptomatic, COPD.<sup>66-80, 82</sup> Three of these trials (n=20,058) evaluated inhaled bronchodilators (LAMA, LABA) and/or ICS,<sup>72, 75, 76</sup> and 13 trials (n=3,658).<sup>66-74, 77-80</sup> evaluated non-pharmacologic interventions (i.e., self-management interventions, exercise counseling interventions, supervised exercise and pulmonary rehabilitation interventions, and clinician education interventions).<sup>66-71, 73, 74, 77-80</sup>

One large RCT (SUMMIT) (n=16,590) demonstrated that LABA, ICS or LABA/ICS could reduce the annual rate of exacerbations in adults with fairly symptomatic (i.e., mean SGRQ score 45-46 or CAT score 18-19) moderate COPD (i.e., mean FEV<sub>1</sub> 59.7% predicted) with a median followup of 1.8 years.<sup>76, 83</sup> Subgroup analyses of another RCT (UPLIFT) demonstrated that LAMA could reduce clinically important deterioration (including clinically significant difference in SGRQ and exacerbations) in persons with moderate COPD (i.e., mean FEV<sub>1</sub> 59% predicted) (n=2603)<sup>84</sup> and reduce exacerbations in patients with minimal symptoms (i.e., GOLD category A) (n=357) at 48 months.<sup>85</sup>

Although a large variety of non-pharmacologic interventions were studied, overall, there was no consistent benefit observed across a range of outcomes (i.e., exacerbations, HRQoL, dyspnea,



exercise or physical performance measures, mental health, smoking cessation) at 26 to 104 weeks. Two RCTs (n=114 and 239) evaluated the same exercise-focused web-based intervention in a VA population.<sup>78, 86</sup> Only one of these two trials (n=114) demonstrated a reduction in COPD exacerbations at 65 weeks,<sup>78</sup> the other trial (n=239) found no reduction in a composite outcome of exacerbations and pneumonia at 52 weeks.<sup>86</sup> Other trials, not conducted in the US, evaluating more intensive self-management interventions, supervised exercise, and pulmonary rehabilitation interventions in persons with mild to moderate COPD, or minimal symptoms, did not demonstrate a reduction in exacerbations or other outcomes. One cluster RCT (n=254 patients) evaluating clinician education/training demonstrated an increase in influenza vaccination, but not pneumococcal vaccination or other outcomes at 52 weeks (Chapter 4: Discussion).<sup>80</sup> It is unclear if and how small sample sizes, usual care comparators in trials conducted outside the US, and/or poor adherence to the interventions contributed to the largely null findings of these trials.

## Included Studies

### Pharmacologic Interventions

We found three studies with newly published analyses in mild to moderate COPD, or minimally symptomatic persons (i.e., GOLD category A) since the 2016 recommendation (**Tables 3 and 4**). Two studies (PINNACLE and SUMMIT) evaluated LABAs, two studies (PINNACLE and UPLIFT) evaluated LAMAs, one study (PINNACLE) evaluated LABA/LAMA, and one study (SUMMIT) evaluated ICS with or without LABA.

The included PINNACLE study was actually a post-hoc analysis of GOLD category A patients (n=729) in three PINNACLE trials (PINNACLE 1, PINNACLE 2, PINNACLE 4) (n=4983).<sup>72</sup> These trials evaluated glycopyrrolate (LAMA), formoterol fumarate (LABA), and glycopyrrolate/formoterol fumarate (LAMA/LABA) versus placebo. Of note, participants on a stable dose of ICS were allowed to continue this therapy. In this subgroup analysis, the mostly male population had a mean age of 65.5 years, and a mean pack year history of 45.6 years, but a low symptom score (i.e., CAT mean score 6.5) consistent with GOLD category A classification.

The SUMMIT trial (n=16,590) evaluated vilanterol (LABA), fluticasone furoate (ICS), and vilanterol/fluticasone furoate (LABA/ICS) versus placebo.<sup>76, 83</sup> All background LABA, LAMA, and ICS were discontinued prior to the trial. In this trial, all participants had to have known cardiovascular disease (CVD) or be at increased risk for CVD (as defined by taking medication for more than 2 cardiovascular risk factors). In this trial, the mostly male population had a mean age of 65 years, mean pack year history of 41 years, mean FEV<sub>1</sub> of about 60 percent predicted, and a fairly high symptom score (i.e., SGRQ 45-56, CAT 18-19).

The UPLIFT trial (n=5993)<sup>75</sup> was included in the previous systematic review that supported the 2016 recommendation, but had 2 newly published post-hoc subgroup analyses in adults with moderate COPD (Stage II) (n=2603)<sup>84</sup> and GOLD category A patients (n=357).<sup>85</sup> UPLIFT evaluated tiotropium (LAMA) versus placebo. Patients were allowed to continue all background medication except for other muscarinic antagonists. In the included subgroup analyses for this trial, the mostly male population had a mean age of 65 years, and a mean pack year history of about 47 years. In the subgroup analysis in adults with moderate COPD, the mean FEV<sub>1</sub> was 59

percent predicted with a fairly high symptom score (i.e., SGRQ 41.5).<sup>84, 87</sup> In the GOLD category A subgroup analysis, the mean FEV<sub>1</sub> was 60.4 percent predicted but the mean symptom score was lower (i.e., SGRQ 16.8).<sup>85</sup>

Although these trials were well conducted multisite RCTs, a few limitations are worth noting. The population studied in SUMMIT is less generalizable to screen-detected populations (i.e., greater degree of airflow obstruction and symptoms), and this trial did not include subgroup analyses of less symptomatic participants as the trial's inclusion criteria specified a symptom score of greater than or equal to 2 on the mMRC. While both PINNACLE and UPLIFT include subgroup analyses or populations more generalizable to screen-detected persons, all were post hoc analyses and only the subgroup analysis of GOLD category A participants in the UPLIFT trial reported interaction testing and controlled for potential confounders (**Table 5**).<sup>85</sup> However, this subgroup analysis of GOLD category A participants only included 357 participants. Last, the PINNACLE trials were limited to 24-week followup.

## **Non-Pharmacologic Interventions**

We found 13 trials evaluating non-pharmacologic interventions used in the management of mild to moderate COPD, or minimally symptomatic persons (i.e., GOLD category A): seven trials of self-management interventions, one trial of exercise-only counseling, three trials of intensive supervised exercise or pulmonary rehabilitation, and two trials of clinician education/training on COPD care (**Tables 6 and 7**).

### *Self-Management Interventions*

Three trials (n=165 to 577) evaluated in-person or phone-based (as opposed to web-only) self-management interventions.<sup>67, 69, 79</sup> Although each of the interventions was different, self-management generally included education on COPD, medications, healthy lifestyle (including but not limited to exercise), tobacco cessation, and an exacerbation management/action plan. These interventions ranged from two to four in-person or phone sessions over several weeks with or without followup calls. The comparator groups received usual care or non-tailored written education materials. These trials included both male and female populations with a mean age ranging from 64.9 to 70.4 years, and 23 to 30 percent of the populations included were active smokers. The trial by Jolly and colleagues (n=577),<sup>69</sup> conducted in the UK, explicitly recruited minimally symptomatic persons with COPD (MRC score 1 or 2), and the mean FEV<sub>1</sub> was 71.7 percent predicted, with a mean SGRQ of 28.7. Nonetheless, almost half of the included population had one or more exacerbations in the previous year. In the other two trials, conducted in the Netherlands, the mean FEV<sub>1</sub>s were lower (60.6 and 65.4 percent).<sup>67, 79</sup>

Another four trials (n=83 to 1325) evaluated a web-only self-management intervention.<sup>73, 77, 78, 86</sup> Two trials evaluated interactive web-based self-management interventions broadly inclusive of topics addressed in the in-person self-management interventions; however, two trials conducted in the VA setting in the United States focused primarily on exercise ('step count') although included some information on disease self-management, self-efficacy, and an online community forum for support.<sup>78, 86</sup> The comparator groups received usual care and/or a pedometer with exercise information. These trials included both male and female populations with a mean age

ranging from 57.6 to 68.6 years, and 19 to 37 percent of the populations included were active smokers. One trial by Voncken-Brewster and colleagues (n=1325), conducted in the Netherlands, recruited both person with COPD and at risk for COPD, 67.6 percent of whom had an MRC score of 1 or 2; however, the mean FEV<sub>1</sub> was not reported.<sup>77</sup> In the other two trials the mean FEV<sub>1</sub> was 60.0 to 62.6 percent.<sup>73, 78</sup>

### *Exercise Only Counseling*

One trial (n=48 in primary care arm) by Altenburg and colleagues, conducted in the Netherlands, evaluated an in-person counseling intervention in which participants were randomized to receive five 30-minute sessions on improving physical activity or usual care. In this trial, the mostly male population had a median age of 65 years, a median pack year history of 30 years, and median FEV<sub>1</sub> of 78 percent predicted.<sup>66</sup>

### *Supervised Exercise or Pulmonary Rehabilitation*

One trial (n=90) by Fastenau and colleagues, conducted in the Netherlands, evaluated an intensive in-person supervised exercise intervention in which participants were randomized to receive twice weekly sessions (60 to 90 min) for 17 weeks or a low intensity session (30 min) once weekly. In this trial, the population was about half male and had a mean age of 62.5 years; 38 percent were current smokers. The mean FEV<sub>1</sub> was 74.2 percent predicted.<sup>68</sup>

Two trials evaluated pulmonary rehabilitation programs; one trial (n=272) evaluated a home-based program,<sup>70</sup> while the other trial (n=71) evaluated an intensive in person program.<sup>74</sup> The trial by Liang and colleagues, conducted in Australia, evaluated an 8-week home-based pulmonary rehabilitation program involving one home visit and followup calls supplemented by a one-time in home pharmacist medication review and smoking cessation session (90 minutes) versus usual care with non-tailored written educational material. In this mostly male population, the mean age was 64.5 years, 61 percent were current smokers, and the mean FEV<sub>1</sub> was 70.0 percent predicted.<sup>70</sup> The other trial by Roman and colleagues, conducted in Spain, evaluated an intensive in-person pulmonary rehabilitation program consisting of three 60 minute sessions a week for 3 months with or without weekly sessions during months 4 through 12, versus usual care. This program also included counseling on medication and smoking cessation. In this mostly male population, the mean age was 64.2 years, and 34 percent were current smokers. This trial recruited only patients with moderate COPD, and the mean FEV<sub>1</sub> was 60.3 percent predicted.<sup>74</sup>

### *Clinician Education Only Interventions*

While some of the included trials implicitly or explicitly provided clinician education as part of the execution of the trial, for most trials, the primary intervention was directed at the patient, and not the clinician. However, two cluster randomized trials (n=216 to 254) conducted outside the United States evaluated clinician education and training for COPD, primarily aimed at general practitioners.<sup>71, 80</sup> One trial by Zwar and colleagues, conducted in Australia, explicitly included persons with COPD identified via active case finding, and therefore also included training aimed at practice nurses to conduct case finding.<sup>80</sup> As such, this trial tended to include persons with less severe symptoms (mean SGQR 19.5, CAT 10.2) and airflow obstruction (mean FEV<sub>1</sub> 74.6

percent predicted). The other trial by Markun and colleagues also included persons with less severe symptoms (69 percent with GOLD category A or B, mean CAT 10.6) and airflow obstruction (mean FEV<sub>1</sub> 67.3 percent predicted).<sup>71</sup>

All the included trials were fair quality without significant threats to validity. However, many of the trials had characteristics that may limit the ability to detect a true benefit (type II error): 1) small trials with a limited number of participants per intervention arm, 2) usual care (most trials were conducted outside the US) or control groups receiving more care than may typically be delivered in the US, and 3) poor adherence to or uptake of the intervention itself.

## Detailed Results

### Pharmacologic Interventions

Two of the three included trials demonstrated that LABA, ICS or LABA/ICS could reduce exacerbations in persons with fairly symptomatic moderate COPD and that LAMA could reduce exacerbations in patients with minimal symptoms (i.e., GOLD category A) (**Table 9**).

The analysis from the PINNACLE trials evaluating glycopyrrolate (LAMA), formoterol fumarate (LABA), and glycopyrrolate/formoterol fumarate (LAMA/LABA) versus placebo in GOLD category A patients (n=729) only reported mortality outcomes and adverse outcomes at 24 weeks. This pooled analysis found no difference in mortality outcomes.<sup>72</sup> Harms are discussed in Key Question 3.

The SUMMIT trial (n=16,590) in persons with mild to moderate COPD (mean FEV<sub>1</sub> 59.7 percent, SGRQ 45-46) found that vilanterol (LABA), fluticasone furoate (ICS), and vilanterol/fluticasone furoate (LABA/ICS) all reduced moderate to severe COPD exacerbations and hospitalizations for exacerbations compared to placebo at a median followup of 1.8 years.<sup>76, 83</sup> In this population, 39.2 percent of persons had a least one exacerbation in the year prior to trial recruitment. The percent reduction in the annual rate of moderate to severe exacerbations was higher for LABA/ICS (29 percent [95% CI, 22 to 35%]) than for LABA (10 percent [95% CI, 2 to 18%]) or ICS (12 percent [95% CI, 4 to 19%]) alone. This trial also found that LABA alone reduced pneumonias compared placebo at a median of 1.8 years, discussed in Key Question 3.

The UPLIFT trial subgroup analysis in moderate (stage II) COPD (n=2603) found that tiotropium (LAMA) reduced clinically important deterioration at 48 months compared to placebo (deterioration was a composite outcome of a decrease in trough FEV<sub>1</sub> of  $\geq 100$  mL, increase in SGRQ total score from baseline  $\geq 4$  units [clinically meaningful difference], or moderate/severe exacerbation).<sup>84</sup> Of note, these results are consistent with prior subgroup analyses by stage and FEV<sub>1</sub> included in the previous review and do not add any new understanding of the benefits of tiotropium over placebo in this population.<sup>87, 88</sup> Another subgroup analysis in GOLD category A patients (n=357) did demonstrate that LAMA reduced the proportion of persons with exacerbations compared to placebo at 48 months, which decreased to 48.4 percent compared to 54.4 percent (RR 0.64 [95% CI, 0.47 to 0.89]).<sup>85</sup> The overall symptom score in these patients was low (i.e., SGRQ 16.8), although the severity of airflow obstruction (FEV<sub>1</sub> 60.4 percent) was similar to those in the moderate (stage II) COPD subgroup analyses.

## Non-Pharmacologic Interventions

### *Self-Management Interventions*

Overall, there were no consistent and significant benefits in outcomes across the four trials evaluating in person or phone-based self-management interventions. However, intervention intensity, outcomes reported, and duration of followup varied across the trials. Neither of the two trials evaluating exacerbation outcomes found a statistically significant difference in exacerbations or hospitalizations at 52 or 104 weeks<sup>67, 69</sup> (**Table 10**). All three trials reported disease specific or general HRQoL outcomes using different instruments (i.e., CRQ, SGRQ, CCQ, and EQ-5D); nonetheless, no trial demonstrated a clinically meaningful or statistically significant benefit in HRQoL at 26, 39 or 104 weeks (**Table 11**). And all three trials reported dyspnea outcomes using either the CRQ (dyspnea domain) or MRC instrument (**Table 12**). Across the trials there were no statistically significant improvements in dyspnea at 26, 39 or 52 weeks; however, in the trial by Bischoff and colleagues (n analyzed=110), the dyspnea outcome improved in the intervention group that received a non-tailored self-management support at 104 weeks (mean difference 0.40 [95% CI, 0.041 to 0.78]).<sup>67</sup> The clinical significance of this finding is unclear, given the small change on a continuous measure and in the setting of no impact on the overall CRQ instrument. In addition, the trial by Jolly and colleagues reported other mental health, exercise, and smoking cessation outcomes, finding no statistically significant improvements in anxiety/depression (data not shown), objective measures of exercise, or smoking cessation at 26 or 52 weeks (**Tables 13 and 14**).<sup>69</sup>

Overall, there were no consistent benefits seen in outcomes across the four RCTs evaluating web-based self-management interventions. Only one exercise-focused web-based intervention did demonstrate a reduction in exacerbations (**Table 10**). Two trials evaluated the same web-based self-management intervention which focused primarily on exercise ('step count').<sup>78, 86</sup> The initial trial by Moy and colleagues (n analyzed=238) found no difference in exacerbations or pneumonia at 52 weeks;<sup>86</sup> whereas the second trial by Wan and colleagues (n analyzed=109)<sup>78</sup> reported a reduction in exacerbations at 65 weeks in participants randomized to the web-based intervention versus the pedometer only group (relative risk [RR] 0.51 [95% CI, 0.31 to 0.85]).<sup>78</sup> The absolute reduction in exacerbations is not reported, but at baseline, the mean (standard deviation) rate of COPD exacerbations in the prior year was 0.42 (0.98) in the intervention group and 0.27 (0.63) in the pedometer only group. All four trials reported disease-specific or general HRQoL outcomes using different instruments (i.e., CAT, CCQ, SGRQ, and EQ-5D); nonetheless, no trial demonstrated a clinically meaningful or statistically significant benefit in HRQoL at 26 or 52 weeks (**Table 11**).<sup>73, 77, 78, 86</sup> Two trials reporting dyspnea outcomes using either the MRC or modified version of the instrument found no statistically significant benefit at 26 or 52 weeks (**Table 12**).<sup>73, 77</sup> All four trials reported objective measures of exercise and found no improvement in exercise outcomes at 26 or 52 weeks, including both trials evaluating the exercise-focused web-based intervention (**Table 13**).<sup>73, 77, 78, 86</sup> In addition, one trial found no benefit in smoking cessation at 26 weeks, using a variety of measures (**Table 14**).<sup>77</sup>

### *Exercise Only Counseling*

One trial by Altenburg and colleagues found no statistically significant benefit on HRQoL (using

the CCQ, CRQ), or on objective measures of global physical performance (using the 6MWT) at 65 weeks for an in-person exercise counseling intervention (**Tables 11 and 13**). This study did not report any exacerbation or dyspnea outcomes.<sup>66</sup>

### *Supervised Exercise or Pulmonary Rehabilitation*

Overall, there were no benefits in reported outcomes across the three trials evaluating supervised exercise or pulmonary rehabilitation interventions. Only one of these trials reported on exacerbations and found no reduction in exacerbations at 52 weeks (**Table 10**).<sup>74</sup> All three trials reported disease specific HRQoL outcomes using different instruments (i.e., CAT, CCQ, SGRQ); none of the trials demonstrated a clinically meaningful or statistically significant benefit in HRQoL at 26 or 52 weeks (**Table 11**).<sup>68, 70, 74</sup> None of the three trials reporting dyspnea outcomes using the CRQ (dyspnea domain), MRC or modified MRC instrument found a statistically significant benefit at 26 or 52 weeks (**Table 12**).<sup>68, 70, 74</sup> One trial by Liang and colleagues reporting mental health outcomes found no improvement in depression and anxiety scores at 26 and 52 weeks (data not shown).<sup>70</sup> Two trials reporting objective measures of physical performance found no improvement in the 6MWD at 26 and 52 weeks (**Table 13**).<sup>68, 74</sup>

### *Clinician Education Only Interventions*

Overall, there were no benefits in reported outcomes in the two cluster RCTs evaluating clinician education and training interventions; however, one trial by Zwar and colleagues (n analyzed= 222) did demonstrate a statistically significant increase in influenza but not pneumococcal vaccinations or smoking cessation at 52 weeks (Chapter 4: Discussion).<sup>80</sup> Reporting of patient level outcomes was more limited for these trials as compared to the other included intervention trials. Neither trial found a benefit on disease specific HRQoL outcomes as measured by the CAT at 52 weeks (**Table 11**).

## **KQ3. What Are the Adverse Effects of COPD Treatments in This Population?**

### **Summary of Results**

Overall, there was very limited included evidence on the harms of pharmacologic and non-pharmacologic interventions in the treatment of mild to moderate, or minimally symptomatic COPD. None of the included trials (i.e., LAMA, LABA, LABA/LAMA or ICS with or without LABA, self-management intervention) that reported adverse effects (six trials) found significant harms. However, the small number of included participants and limited length of followup in the included trials (or their relevant subgroup analyses) limits the ability to detect uncommon harms or longer-term harms. Given this update's focus on screen-relevant populations, only two large observational studies addressing harms of pharmacologic treatment met our inclusion criteria. These studies demonstrated that initiation of LAMA or LABA may increase the risk of a serious cardiovascular event in treatment naïve patients and that ICS may increase the risk of developing diabetes. However, these observational studies are a subset of a much larger body of evidence on serious harms of bronchodilators and ICS in COPD (Chapter 4: Discussion).

## Included Studies

### Pharmacologic Interventions

The three included trials from Key Question 2 also report adverse effects (**Tables 3 and 4**).<sup>72, 76, 83-85, 87, 88</sup> Two trials (PINNACLE and SUMMIT) evaluated LABAs, two trials (PINNACLE and UPLIFT) evaluated LAMAs, one trial (PINNACLE) evaluated LABA/LAMA, and one trial (SUMMIT) evaluated ICS with or without LABA. For a description of these trials, see Key Question 2: Included studies section.

In addition to these three trials, we also found two observational studies evaluating the harms of LABA, LAMA, or ICS in screen-relevant populations (**Table 16**). One nested case-control study in Taiwan by Wang and colleagues examined the cardiovascular risk for the initiation of LABA and LAMA in treatment naïve COPD patients.<sup>82</sup> The other study was a matched cohort study in the UK by Price and colleagues which examined the risk of diabetes and osteoporosis from ICS use in populations in whom the majority of patients were stage I or II and GOLD category A or B.<sup>81</sup> The mean age in the observational studies was slightly older than the trial populations. The mean FEV<sub>1</sub> or symptom score was not reported, nonetheless the studies provided some indication of severity of COPD. The study by Price and colleagues conducted subgroup analysis for GOLD categories A and B patients.<sup>81</sup> The vast majority of studies evaluating harms of pharmacologic treatment were excluded because no description was reported regarding the severity or symptoms of included populations. Both of these studies used large nationally representative databases and tried to adjust for known confounders.

### Non-Pharmacologic Interventions

Only three of the included non-pharmacologic intervention trials from Key Question 2 also reported on harms.<sup>69, 78, 86</sup> We found no additional studies that specifically evaluated the harms of non-pharmacologic interventions in a screen-relevant population. All three trials evaluated self-management interventions. One trial by Jolly and colleagues (n=577) conducted in the UK, explicitly recruited minimally symptomatic persons with COPD (MRC score 1 or 2) and evaluated a phone-based intervention. The other two trials by Moy and colleagues (n=238) and by Wan and colleagues (n=114) were conducted in VA settings and included more symptomatic persons and evaluated an exercise-focused web-based intervention. For additional details of these trials, see Key Question 2: Included studies section.

## Detailed Results

### Pharmacologic Interventions

Overall, none of the included trials found significant harms for LAMA, LABA, LABA/LAMA, or ICS with or without LABA (**Table 15**). However, the subgroup analyses from PINNACLE and UPLIFT included a limited number of participants and therefore are quite limited in their ability to detect less common harms, and both PINNACLE and SUMMIT have limited length of followup and therefore are limited in their ability to detect longer term harms.

The analysis from the PINNACLE trials evaluating glycopyrrolate (LAMA), formoterol fumarate (LABA), and glycopyrrolate/formoterol fumarate (LAMA/LABA) versus placebo in GOLD category A patients (n=729) reported adverse outcomes at 24 weeks.<sup>72</sup> This pooled analysis across three trials did not report any statistically significant harms. There is a signal of increased serious adverse events related to study treatment for LABA/LAMA compared to placebo (1.8 percent versus 0.9 percent), but this was based on a total of 5 adverse events across both arms.

The SUMMIT trial (n=16,590) in persons with mild to moderate COPD (mean FEV<sub>1</sub> 59.7 percent, SGRQ 45-46) found that vilanterol (LABA), fluticasone furoate (ICS), and vilanterol/fluticasone furoate (LABA/ICS) did not increase adverse events compared to placebo at a median followup of 1.8 years.<sup>76, 83</sup> This trial did not find an increase in pneumonias from ICS with or without LABA. In fact, this study demonstrated that LABA alone reduced pneumonias compared to placebo at a median of 1.8 years, 3.9 versus 5.2 percent (HR 0.72 [95% CI, 0.59 to 0.89]).

The subgroup analyses from the UPLIFT trial did not report any increase in adverse events from tiotropium (LAMA) versus placebo at 48 months.<sup>84, 85, 87, 88</sup> However, in the subgroup analysis of GOLD category A patients (n=357), there is a signal of increased major adverse cardiac events from LAMA compared to placebo (5.9 percent versus 1.8 percent), but this was based on a total of 14 adverse events across both arms.<sup>85</sup>

The nested case-control study by Wang and colleagues (n=37,719 cases and 146,139 controls) observed that the initiation of both LABA and LAMA was associated with an increase in cardiovascular events within 30 days of its initiation (OR 1.50 [95% CI, 1.35 to 1.67 and adj OR 1.52 [95% CI, 1.28 to 1.80], respectively). However, notably this risk association was absent, or even reduced, with prevalent use. Risk of cardiovascular events did not seem to vary by different LABA or LAMA drugs, concomitant COPD medications, history of CVD, or history of prior COPD exacerbations (**Table 16**).<sup>82</sup>

The matched cohort study by Price and colleagues (n= 17,970 for diabetes onset and n= 19,898 for osteoporosis onset) observed that long-term ICS use, compared with long-acting bronchodilator use, was associated with an increased risk of developing diabetes (HR 1.27 [95% CI, 1.07 to 1.50]). The subgroup analysis conducted in GOLD categories A and B patients combined had similar findings (**Table 16**). The study also noted a dose-response relationships at mean ICS exposures of 500 µg/day or greater versus less than 250 µg/day, fluticasone propionate-equivalent.<sup>81</sup> The association with an increased risk of developing osteoporosis was not statistically significant and not observed in the subgroup analysis in GOLD categories A and B patients.

## Non-Pharmacologic Interventions

The RCT by Jolly and colleagues (n=577) reported no difference in self-reported adverse events at 52 weeks between the phone-based intervention compared to the usual care group (24 versus 20 events, p value NR).<sup>69</sup> The RCT by Moy and colleagues (n=238) reported no difference in pulmonary or cardiac adverse events between the web-based intervention and pedometer only



groups; however, more minor musculoskeletal adverse events occurred in the intervention group (27.9%) than the pedometer group (10%).<sup>86</sup> The RCT by Wan and colleagues (n=114) reported no statistically significant difference in adverse events at 13 weeks between the group receiving the web-based intervention compared to the pedometer only group (14 versus 10 events, p=0.54 respectively).<sup>78</sup> In all of the trials, none of the serious adverse events were determined to be related to the study intervention.

# Chapter 4. Discussion

## Summary of Findings and Comparison to Last Review

### Effectiveness of Screening for COPD

To date, there are still no completed studies evaluating the effectiveness of screening or active case finding for COPD on patient health outcomes (i.e., improves COPD morbidity, mortality or HRQoL) (**Table 17**). However, there are many studies, not included in this review, that demonstrate that active case finding (i.e., systematically assessing for symptoms and/or risk factors and performing spirometry) can identify persons yet undiagnosed with COPD, the vast majority of which are single arm or uncontrolled studies evaluating the yield of COPD.<sup>89-94</sup> Comparative studies evaluating systematic screening approaches demonstrate that active case finding identifies more COPD than usual care.<sup>89, 95-97</sup> Overall these studies, mostly conducted outside the US, evaluate a range of approaches (i.e., use of questionnaires, electronic case-finding algorithms, handheld flow meters, coupling spirometry to lung cancer screening, direct invitation to spirometry); regardless of the approach, studies targeting those at higher risk (e.g., based on smoking history, occupational exposure) or those using pre-screening questionnaires can identify many persons with yet undiagnosed COPD. And use of pre-screening questionnaires in case finding can reduce the number of spirometry tests performed.<sup>98</sup>

Currently, there is one cluster RCT, COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE), of screening for COPD underway (**Appendix E Table 1**).<sup>47</sup> This trial evaluates screening with a 5-item questionnaire and peak flow measurement in persons ages 45 to 80 years old in primary care, without any restrictions on smoking history. It has a planned 5-year follow-up and includes outcomes on changes to clinical care, patient symptoms, exacerbations, hospitalizations and mortality. This trial is scheduled to be completed in July 2022.

### Treatment of Screen-Relevant COPD

Similar to the previous review's findings, we found no trials of pharmacologic treatment of COPD in screen-detected patients. However, we did identify 16 trials, or subgroup analyses from trials, evaluating the treatment of mild to moderate, or minimally symptomatic, COPD which met our inclusion criteria for screen-relevant COPD (**Table 17**).<sup>66-80, 86</sup> Three of these trials evaluated inhaled bronchodilators (LABA or LAMA) and/or ICS, one of which (UPLIFT) was included in the previous systematic review to support the 2016 recommendation.<sup>75, 76, 82</sup> Overall, the results of these trials and their subgroup analyses are consistent with the previous review's findings that bronchodilators (LABA or LAMA) with or without ICS can reduce COPD exacerbations and LAMA (i.e., tiotropium) can improve HRQoL (as measured by the SGQR) in adults with fairly symptomatic moderate COPD. In 2016, the USPSTF stated that the evidence in these populations (e.g., mean FEV<sub>1</sub> 60 percent predicted) was not widely applicable to persons with COPD identified through screening. In this update, one small subgroup analysis (n=357) of UPLIFT demonstrated that tiotropium compared to placebo can reduce exacerbations in patients with minimally symptomatic moderate COPD at 48 months.

Since the previous review, we have also newly included 13 trials evaluating non-pharmacologic interventions in mild to moderate, or minimally symptomatic, COPD.<sup>66-71, 73, 74, 77-80, 86</sup> Unfortunately, these trials evaluating a range of interventions (i.e., self-management interventions, exercise counseling interventions, supervised exercise and pulmonary rehabilitation interventions, and clinician education interventions) did not demonstrate a consistent benefit across a range of patient outcomes. Only one VA trial (n=114) evaluating a web-based self-management intervention focused on exercise ('step count') found a reduction in COPD exacerbations at 65 weeks in persons with moderate COPD (i.e., mean FEV<sub>1</sub> 63 percent predicted).<sup>78</sup> However, other trials of self-management interventions, supervised exercise, and pulmonary rehabilitation interventions in person with mild to moderate COPD, or minimal symptoms, did not demonstrate a reduction in exacerbations or other outcomes. It is unclear if and how the small samples sizes in these trials, usual care comparators outside the United States (only two US based studies), and/or poor adherence to interventions contributed to the largely null findings observed in these non-pharmacologic intervention trials.

Similar to the previous review, there was very limited included evidence on the harms from included treatment trials. None of the included trials that reported adverse effects found significant harms. However, these trials generally have a limited ability to detect uncommon harms or longer-term harms. Two large observational studies addressing harms of medications demonstrated that initiation of LAMA or LABA may increase the risk of a serious cardiovascular event in treatment-naïve patients and that ICS may increase the risk of developing diabetes.<sup>81, 82</sup> External to this review, meta-analyses of treatment trials examining harms have demonstrated that LABAs, but not LAMAs, may increase cardiovascular events (specifically heart failure).<sup>99, 100</sup> Existing reviews and meta-analyses of treatment trials examining harms of ICS (alone or in combination with LABAs) have demonstrated an increased risk of pneumonia, but these findings may be drug specific.<sup>101, 102</sup>

## **Screening for COPD Impact on Uptake of Smoking Cessation, Vaccinations, and Lung Cancer Screening**

Smoking cessation, vaccinations, and lung cancer screening in persons who meet criteria are important components of disease management for COPD. However, despite guidelines recommending these preventive services, smoking cessation in active smokers (and recidivism after initial cessation),<sup>103</sup> as well as uptake of influenza and pneumococcal vaccination,<sup>104</sup> remain suboptimal. Thus, interventions to increase smoking cessation success and vaccinations in persons with COPD remain an active area of research.<sup>105, 106</sup> Observational studies suggest that a new diagnosis of COPD is linked to smoking cessation, that smokers with COPD are more likely than those without COPD to be advised to quit smoking and offered smoking cessation support and followup, and that persons with symptomatic COPD (i.e., frequent cough, phlegm, wheeze, shortness of breath, higher symptom score) have greater odds of intention to quit smoking.<sup>107-109</sup>

Three included RCTs evaluating non-pharmacologic interventions reported smoking cessation outcomes and did not demonstrate a benefit for self-management interventions or clinician education/training on these outcomes (**Table 14**).<sup>69, 77, 80</sup> We also considered whether identifying undiagnosed COPD might improve the uptake of other recommended preventive services (including but not limited to smoking cessation). In addition to the included trials, six RCTs

(n=2,294) designed to evaluate the incremental benefit of receipt of spirometry results or ‘lung age’ (i.e., to approximate the impact of screening or case finding for COPD on smoking cessation) have not consistently shown that receipt of spirometry results or ‘lung age’ increases smoking cessation (**Tables 17 and 18**).<sup>110-115</sup> Only one of these trials (n=561), conducted in the UK and included in the prior review, evaluating the incremental value of ‘lung age’ to standardized smoking cessation counseling, reported a statistically significant difference in biochemically confirmed abstinence from smoking at 1 year.

Unfortunately, comparative studies to address how identifying COPD impacts other recommended preventive services remain quite limited. Only one included RCT evaluating non-pharmacologic interventions reported on uptake of vaccinations.<sup>80</sup> This cluster RCT by Zwar and colleagues, conducted in Australia, evaluated clinician training on team-based management of COPD. At 52 weeks, 72.8 percent of patients of clinicians in the intervention group, compared to 56.8 percent of patients of clinicians in the control group, were vaccinated for influenza (p=0.035), and 47.9 percent in the intervention group compared to 38.3 percent were vaccinated for pneumococcus; however, results were not statistically significant for pneumococcal vaccination (p=0.15). We found no comparative studies on the incremental benefit of spirometry or diagnosis of COPD on uptake of vaccinations or lung cancer screening.

## Limitations and Future Research Needs

This review was a targeted evidence update aimed at addressing the interval evidence on key evidence gaps identified in the 2016 USPSTF recommendation on Screening for COPD. As such, this review only updated a subset of the key questions previously addressed. This targeted evidence update did not address the screening yield or screening accuracy of various screening or active case-finding approaches. Nonetheless, it is clear from non-comparative and comparative studies that a variety of organized screening approaches in persons at risk for COPD (e.g., risk algorithms, pre-screening questionnaires, handheld devices) can identify yet undiagnosed COPD and more undiagnosed COPD than opportunistic case finding. Likewise, we did not evaluate the screening harms represented by the diagnostic inaccuracy for various screening approaches (i.e., false negatives and false positives). Populations at very high risk for COPD, in whom surveillance for COPD is generally recommended (e.g., persons with alpha-1 antitrypsin deficiency and workers with known occupational exposures) were not included in this review and therefore the findings do not apply to the use of periodic spirometry in occupational settings or specialty care.

Given the absence of direct evidence that screening or active case finding for COPD improves COPD morbidity, mortality, or patient HRQoL, this review focuses on the benefits and harms of treatment in screen-detected populations. Because we found limited intervention trials in these populations, we also included trials that were conducted, or reported subgroup analyses, in persons with mild to moderate COPD or who were minimally symptomatic (based on GOLD criteria). Trials or analyses conducted in populations following an acute COPD exacerbation were also excluded. We acknowledge that persons with more severe airflow obstruction or with greater symptom burden are identified with screening or active case-finding; and that severity of airflow obstruction does not necessarily correlate with symptom burden. This population focus necessarily restricted the number of treatment studies included, which resulted in the lack or

under-representation of certain types of therapies (e.g., combination inhaled therapies, anti-inflammatory therapies, pulmonary rehabilitation). Although we included pulmonary rehabilitation trials aimed at persons with mild to moderate COPD or who were minimally symptomatic, the vast majority of trials evaluating pulmonary rehabilitation are not in these populations. Pulmonary rehabilitation, in general, has been demonstrated to improve exercise capacity, dyspnea, and quality of life in persons with COPD.<sup>116,117</sup> Furthermore, there is evidence to suggest that pulmonary rehabilitation can result in improvement in these outcomes independent of baseline disease burden, such that persons with mild or moderate COPD may benefit similarly to those with more severe airflow obstruction.<sup>118-120</sup> This population focus also restricted the number of studies addressing harms, as most of the observational studies addressing harms of pharmacologic therapies did not report disease or symptom severity. We also *a priori* excluded other intervention types that may have been studied in relevant populations (e.g., acupuncture, neuromuscular electrostimulation, Tai Chi or other active mind-body movement therapies, focused upper limb exercise training).

Our targeted update, as well as the prior review to support the 2016 USPSTF recommendation, focused on the impact of screening and treatment on *a priori* defined health outcomes. We did not include physiologic changes in FEV<sub>1</sub> as an outcome. Currently both GOLD and the American Thoracic Society state that there is not conclusive evidence that pharmacotherapy modifies the long-term decline in lung function<sup>10,121</sup> However, placebo controlled trials of pharmacologic therapies have demonstrated that LAMA (tiotropium), LABA (salmeterol, vilanterol) and ICS (fluticasone, budesonide) can reduce the decline of FEV<sub>1</sub> by about 5mL/year in trials reporting follow-up from 40 to 60 months.<sup>122</sup>

Based on this update, we identify a few important evidence gaps and suggestions for future research. First, we acknowledge that early COPD is not synonymous with mild COPD and that true identification of early disease would allow for intervening at a stage which may prevent pulmonary function impairment or decline.<sup>8</sup> Ongoing research is currently addressing these issues around diagnosis and treatment based on the pathobiological mechanisms (and their biomarkers) to develop and deliver treatment that can modify the natural course of disease, rather than symptom-based treatment.<sup>123</sup>

Second, since airflow obstruction and symptom burden do not necessarily correlate, it is important to characterize populations by both of these dimensions. Many trials report airflow obstruction as a baseline characteristic and subgroup analyses by severity of airflow obstruction. It would be as helpful to have parallel data for symptom burden or by GOLD categories A through D, or using other measures of symptoms. The mMRC is limited to one question on dyspnea and does not capture other symptoms. The 8-item CAT has been shown to be a more effective assessment for symptom severity in COPD patients.<sup>124</sup>

Third, the lack of *consistent* treatment benefit observed in persons with mild to moderate or minimally symptomatic COPD does not mean that treatment cannot benefit these persons. Included trials, and their subgroup analyses, are limited by small samples and single trials/analyses. In patients with low symptom burden, it may be difficult to demonstrate clinically meaningful improvement using current HRQoL or symptom scales due to already low scores (i.e., floor effect), and demonstrating a benefit on morbidity or mortality from COPD may

require longer-term followup (than in current trials) in persons with less severe disease. For many of the non-pharmacologic intervention trials not conducted in the US, the usual care arm may have already been receiving care beyond standard of care in the US, therefore making it more difficult for these trials to show a benefit. Future research should include treatment studies to replicate findings of tiotropium in minimally symptomatic persons using a range of outcomes; trials or (more realistically) well conducted comparative observational studies in persons with minimal symptoms or airflow obstruction evaluating the association of treatment and longer-term COPD morbidity and mortality; and replication of successful non-pharmacologic interventions in US screen-relevant populations. A scan of ongoing studies shows several trials designed to evaluate non-pharmacologic interventions, however, none are in the United States (**Appendix E Table 1**).

Last, to date there are still no comparative studies evaluating the benefit of screening or active case finding on patient health outcomes. Comparative studies evaluating screening or active case finding on yield of COPD diagnoses should include longer-term followup to determine the impact on quality of life, COPD morbidity and mortality, as well as smoking cessation outcomes, and uptake of recommended vaccinations and lung cancer screening. The CAPTURE trial currently underway will provide direct evidence for the effectiveness of screening for COPD in the United States (**Appendix E Table 1**).<sup>47</sup>

## Conclusions

The findings of this targeted evidence update are generally consistent with the findings of the previous systematic review that supported the USPSTF's 2016 recommendation not to routinely screen for COPD. There are still no comparative studies on the effectiveness of screening or active case finding for COPD on patient health outcomes, although one is currently underway. The observed benefits of pharmacologic therapies for COPD are still largely limited to persons with moderate airflow obstruction. There was no consistent benefit of a range of non-pharmacologic interventions in mild to moderate, or minimally symptomatic persons with COPD. In general, harms of pharmacologic and non-pharmacologic interventions are not consistently reported in treatment trials, although large observational studies suggest harms for the initiation of LAMA or LABA and the longer-term use of ICS in persons with COPD.

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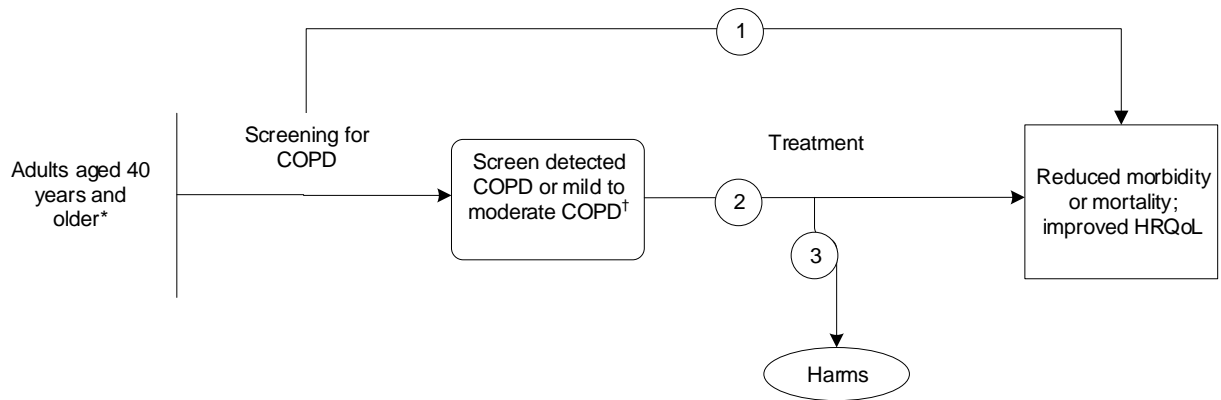
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**Figure 1. Analytic Framework**



\*Asymptomatic adults, adults who have physical symptoms that are undetected by the patient or the clinician, or those who have nonspecific symptoms that have gone unrecognized as being related to COPD

†Mild (forced expiratory volume in one second [FEV1]  $\geq$  80% predicted) to moderate (FEV1 50-79%)

Abbreviations: COPD = Chronic Obstructive Pulmonary Disease, HRQoL = Health-related quality of life

**Table 1. Classification of COPD as Defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD)<sup>4</sup>**

	<b>COPD Classification</b>	<b>Definition</b>
Classification of airflow limitation (post-BD FEV <sub>1</sub> )	Mild GOLD Stage I	FEV <sub>1</sub> ≥80% predicted
	Moderate GOLD Stage II	FEV <sub>1</sub> ≥50% predicted but <80% predicted
	Severe GOLD Stage III	FEV <sub>1</sub> ≥30% predicted but <50% predicted
	Very severe GOLD Stage IV	FEV <sub>1</sub> <30% predicted
Classification of symptoms/risk of exacerbation	GOLD category A	mMRC 0-1 or CAT <10 (low symptom burden) History of 0 or 1 moderate or severe exacerbations (not leading to hospital admission)
	GOLD category B	mMRC ≥ 2 or CAT ≥10 (higher symptom burden) History of 0 or 1 moderate or severe exacerbations (not leading to hospital admission)
	GOLD category C	mMRC 0-1 or CAT <10 (low symptom burden) History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)
	GOLD category D	mMRC ≥ 2 or CAT ≥10 (higher symptom burden) History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)

**Abbreviations:** CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; FEV<sub>1</sub> = forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council questionnaire; post-BD = post bronchodilator.

**Table 2. Selected COPD Guidelines on Screening or Active Case-Finding**

Organization, year	Recommendation
GOLD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2021 <sup>125</sup>	<p>GOLD states that the role of screening spirometry in the general population is controversial.</p> <p>GOLD advocates active case finding, i.e., performing spirometry in patients with symptoms and/or risk factors, but not screening spirometry. Systematic case-finding in a primary care setting via mail-out of a screening questionnaire was also found to be an effective way to identify undiagnosed COPD patients.</p>
United Kingdom National Screening Committee (UK NSC), 2018 <sup>126</sup>	<p>The UK NSC does not recommend screening for COPD because there is not an accurate test to detect early COPD, the best treatment for early COPD is to stop smoking, people with few or no symptoms may not be willing to do this, and it is not known if medicines for COPD are effective in people with mild symptoms.</p> <p>The UK NSC does not mention active case finding.</p>
American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and European Respiratory Society (ERS), 2011 <sup>9*</sup>	<p>The joint panel recommends against screening asymptomatic patients for COPD using spirometry, citing there was no evidence of benefit based on moderate-quality evidence.</p> <p>The panel recommends case finding with spirometry, in patients reporting COPD-related symptoms.</p>

\*Referenced in prior review, no updated recommendation related to screening or case finding found

**Table 3. Key Question 2 Results: Study Characteristics for Included RCTs of Pharmacologic Treatment**

Study, Year Quality	Country	N Randomized	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant therapies allowed
PINNACLE Martinez, 2020 <sup>72</sup>  Fair	International	4983 (full population) GOLD category A subset: 729	24 weeks	40-80 years; smoking history of $\geq 10$ pack-years; Post-BD $FEV_1 < 80\%$ predicted; $FEV_1/FVC \leq 70\%$	Significant diseases other than COPD; pregnant/ lactating women; lung volume reduction surgery within last year; hospitalization due to COPD within 3 months or during screening; smoking status change during screening; long-term oxygen therapy required > 12 hours/day	IG1: LAMA/LABA glycopyrrolate/formoterol fumarate (18/9.6 $\mu\text{g}$ /twice a day) IG2: LAMA glycopyrrolate (18 $\mu\text{g}$ /twice a day) IG3: LABA formoterol fumarate (9.6 $\mu\text{g}$ /twice a day) CG: Placebo	Patients receiving stable dose of ICS at screening were permitted to continue
SUMMIT Vestbo, 2016 <sup>76</sup> Crim, 2017 <sup>83</sup>  Good	International	16,590	4 years*	40-80 years; smoking history of $\geq 10$ pack-years; Post-BD $FEV_1$ 50-70% predicted; $FEV_1/FVC \leq 70\%$ ; score of $\geq 2$ on mMRC dyspnea scale; history or increased risk of cardiovascular disease <sup>†</sup>	Respiratory disorders other than COPD, lung reduction surgery, receiving long-term oxygen, or oral corticosteroid therapy, severe heart failure, life expectancy less than 3 years, and end-stage chronic renal disease	IG1: ICS/LABA fluticasone furoate/vilanterol (100/25 $\mu\text{g}$ /day) IG2: LABA vilanterol (25 $\mu\text{g}$ /day) IG3: ICS fluticasone furoate (100 $\mu\text{g}$ /day) CG: Placebo	All ICS, LABA, and LAMA were discontinued, although other COPD medications such as theophyllines were allowed

**Table 3. Key Question 2 Results: Study Characteristics for Included RCTs of Pharmacologic Treatment**

Study, Year Quality	Country	N Randomized	Followup	Inclusion	Exclusion	Treatment Comparison	Concomitant therapies allowed
UPLIFT Decramer, 2009 <sup>87</sup> † Tashkin, 2012 <sup>88</sup> ‡ Tashkin, 2008 <sup>75</sup> † Halpin, 2015 <sup>85</sup> Rabe, 2020 <sup>84</sup>  Fair	International	5993 (full population) <sup>75</sup> Stage II subset: 2739 <sup>84, 87</sup> FEV <sub>1</sub> ≥60% subset: 1210 <sup>88</sup> GOLD category A subset: 357 <sup>85</sup>	4 years	≥ 40 years; smoking history of ≥10 pack-years; Post-BD FEV <sub>1</sub> <70% predicted; FEV <sub>1</sub> /FVC≤70%§	History of asthma, COPD exacerbation or respiratory infection within 4 weeks before screening, a history of pulmonary resection, long-term oxygen therapy required > 12 hours/day	IG: LAMA tiotropium bromide (18 µg/day) CG: Placebo	All respiratory medications except other SAMA or LAMA

\* Maximum followup was 4 years; median study exposure was 1.8 years (IQR 1.2-2.6) and was similar across treatment groups

† Cardiovascular disease was defined as coronary artery disease, peripheral arterial disease, stroke, myocardial infarction, or diabetes mellitus with target organ disease. Increased cardiovascular risk was defined as aged 60 years or older and receiving medication for more than two of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease. 182 pts failed to meet cardiovascular entry criteria but were included in analysis.

‡ Included in previous report<sup>127</sup>

§ 23 patients had FEV<sub>1</sub>>70 (protocol violation) but included in the analysis

**Abbreviations:** CG = control group; COPD = chronic obstructive pulmonary disease; FEV<sub>1</sub> = forced expiratory volume in one second; FVC = Forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; IG = intervention group; LABA = long acting beta agonist; LAMA = long acting muscarinic antagonist; MRC = medical research counsel; mMRC = Modified Medical Research Counsel questionnaire; µg = microgram; N = number of participants; post-BD = post bronchodilator; SUMMIT = study to understand mortality and morbidity in COPD; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium.

**Table 4. Key Question 2 Results: Population Characteristics for Included RCTs of Pharmacologic Treatment**

Study, Year	N Randomized	Age, years (mean)	Female, %	Smoking status, %	Smoking history, pack-years (mean)	Number of exacerbations in the preceding year	Lung function post-BD FEV <sub>1</sub> % predicted of normal (mean)	HrQOL symptom score
PINNACLE Martinez, 2020 <sup>72</sup>	GOLD A subset: 729	65.5	27.3%	Current: 32.8%; Former: 67.2%	45.6	NR	NR	CAT mean score: 6.5
SUMMIT Vestbo, 2016 <sup>76</sup> Crim, 2017 <sup>83</sup>	Full population: 16,590	65	25.5%	Current: 46.6%; Former: 53.4%	41	1: 24.4% 2 or more: 14.8%	59.7	SGRQ total score mean: 45-46; CAT mean score: 18-19
UPLIFT Decramer, 2009 <sup>87</sup>	Stage II subset: 2,739	64.5	NR	Current: 33.0%; Former: 67.0%	47.5	NR	59	SGQR total score mean: 41.5
Tashkin, 2012 <sup>88</sup> Tashkin, 2008 <sup>75</sup> Halpin, 2015 <sup>85</sup> Rabe, 2020 <sup>84</sup>	FEV <sub>1</sub> ≥60% subset: 1,210	64	29.9%	Current: 32.3%; Former: 67.7%	47.6	NR	64	SGQR total score mean: 40
	GOLD category A: 357	65	18.5%	Current: 29.4%; Former: 70.6%	NR	NR	60.4	SGQR total score mean: 16.8

**Abbreviations:** CAT= COPD Assessment Test; FEV<sub>1</sub> = forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; µg = microgram; N = number of participants; NR = not reported; postBD = post bronchodilator; RCT = randomized controlled trial; SGRQ = St George's Respiratory Questionnaire; SUMMIT = study to understand mortality and morbidity in COPD; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium.

**Table 5. Key Question 2 Results: Subgroup Credibility Ratings for RCTs of Pharmacologic Treatment**

Study, year	Subgroup	Timing of analysis	Interaction testing performed?	Groups matched at baseline?	Controlled for confounders?
PINNACLE Martinez, 2020 <sup>72</sup>	GOLD category A	Post-hoc*	No†	Yes	No†
UPLIFT Decramer, 2009 <sup>87</sup>	COPD Stage II	A-priori	Yes (for exacerbations only)	Yes	No
UPLIFT Tashkin, 2012 <sup>88</sup>	FEV <sub>1</sub> ≥60% predicted	Post-hoc	No	Only difference is statistically significantly more smokers in CG than IG (36% versus 29% P=0.011)	For HrQOL analysis only
UPLIFT Halpin, 2015 <sup>85</sup>	GOLD category A	Post-hoc	Yes	Yes	Yes
UPLIFT Rabe, 2020 <sup>84</sup>	COPD Stage II	Post-hoc	No	NR	NR

\* The analyses of lung function by GOLD category were specified in an integrated statistical analysis plan that was developed after the reporting of data from PINNACLE-1 and -2, but prior to the unblinding of PINNACLE-4.

† Performed for lung function outcomes but not for mortality or harms

‡ Included in previous report<sup>127</sup>

§ 23 patients had FEV<sub>1</sub>>70 (protocol violation) but included in the analysis

**Abbreviations:** CG = control group; COPD = chronic obstructive pulmonary disease; FEV<sub>1</sub> = forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HrQOL = health-related quality of life; IG = intervention group; NR = not reported; SUMMIT = study to understand mortality and morbidity in COPD; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium.

**Table 6. Key Question 2 Results: Study Characteristics for Included Trials of Non-Pharmacologic Treatments**

Intervention type	Author, Year Study*	Country	Design	N Randomized	Followup	Inclusion	Exclusion
Self-management	Bischoff, 2012 <sup>67</sup>	Netherlands	RCT	165	104 weeks	Aged 35 years and older and FEV <sub>1</sub> /FVC < 0.70	Post-BD FEV <sub>1</sub> < 30% predicted, treatment by a respiratory physician, severe comorbid conditions with a reduced life expectancy, inability to communicate in the Dutch language
	Jolly, 2018 <sup>69</sup> PSM COPD	United Kingdom	RCT	577	52 weeks	≥18 years, on the practice COPD register, mild dyspnea (MRC grades 1 or 2), FEV <sub>1</sub> /FVC < 0.7	Considered to be inappropriate for the study by patients' physician (e.g., terminal disease or a severe psychiatric disorder)
	Moy, 2016 <sup>86</sup> Taking Healthy Steps	United States	RCT	239	52 weeks	≥ 40 year; diagnosis of COPD, emphysema, or chronic bronchitis based on administrative ICD-9 codes; able to walk a minimum of one block; sedentary (defined by < 150 minutes of self-reported physical activity per week); physician clearance; regular email user with internet access	Quadriplegia/paraplegia or wheelchair dependence, dementia, pregnancy-related diagnoses/procedures in past year, involvement in another pedometer walking program
	Nyberg, 2019 <sup>73</sup>	Sweden	CCT	83	52 weeks	Diagnosis of COPD	Inability to communicate in Swedish
	Voncken-Brewster, 2015 <sup>77</sup> MasterYourBreath	Netherlands	RCT	1325	26 weeks	Diagnosed with COPD or at moderate/high risk for COPD, aged 40–70, internet access and basic computer skills	Inability to communicate in the Dutch language
	Wan, 2020 <sup>78</sup> ESC	United States	RCT	114	65 weeks	Aged ≥40 years, ≥10 pack-years of smoking, FEV <sub>1</sub> /FVC < 0.70 or emphysema on a CT, able to walk one block, internet access and basic computer skills, >90% accuracy on step counter	COPD exacerbation requiring prednisone or antibiotics in past month, inability to ambulate, unstable CVD or congestive heart failure, pulmonary rehabilitation in previous three months, plans to participate in another exercise study or program in next 3 months, <85% blood oxygen saturation during 6MWT



**Table 6. Key Question 2 Results: Study Characteristics for Included Trials of Non-Pharmacologic Treatments**

Intervention type	Author, Year Study*	Country	Design	N Randomized	Followup	Inclusion	Exclusion
	Weldam, 2017 <sup>79</sup> COPD-GRIP	Netherlands	Cluster RCT	204	39 weeks	Diagnosed with COPD, age ≥40, a lung function test in previous year	Life-threatening comorbid condition or if they had a primary diagnosis of asthma, inability to communicate in the Dutch language
Exercise only	Altenburg, 2015 <sup>66</sup> COACH	Netherlands	RCT	48 <sup>†</sup>	65 weeks	Age 40-80, COPD diagnosed based on GOLD guidelines	Comorbidities which severely limit physical activity, exacerbations or respiratory tract infections within prior two months
Supervised exercise or pulmonary rehabilitation	Fastenau, 2020 <sup>68</sup>	Netherlands	RCT	90	26 weeks	Mild to moderate COPD, dyspnea, and physically inactive lifestyle	Pulmonary rehabilitation in the past year, lower respiratory tract infections in past 8 weeks, serious comorbid conditions
	Liang, 2019 <sup>70</sup> RADICALS	Australia	Cluster RCT	272	52 weeks	≥40 years, at least two clinic visits in past year, COPD diagnosed based on spirometry and clinical confirmation	NR
	Roman, 2013 <sup>74</sup>	Spain	RCT	71	52 weeks	35 to 74 years old, moderate COPD based on GOLD guidelines	Musculoskeletal conditions that prevented exercising and walking test assessments, or terminal illness or other severe disease
Clinician education only	Markun, 2018 <sup>71</sup> CAROL	Switzerland	Cluster RCT	216	52 weeks	≥45 years, ≥10 pack-years smoking history, FEV <sub>1</sub> /FVC<0.7	Patients attending for emergency consultations, insufficient German language skills, asthma/hay fever, estimated life expectancy <6 months
	Zwar, 2016 <sup>80</sup> PELICAN	Australia	Cluster RCT	254	52 weeks	Attended the practice at least twice (once in past 12 months); risk factors for COPD (aged 40-85 years and history of smoking); COPD identified via case finding by study nurse based on 2005 ATS/ERS guidelines	Previously recorded diagnosis of COPD, Inability to communicate in English, cognitive impairment

\* All studies fair quality.

† Respiratory Health Screening Questionnaire score >19.5

‡ Primary care arm only

**Abbreviations:** 6MWT = six minute walk test; ATS/ERS = American Thoracic Society and European Respiratory Society (ERS); CAROL = Care in Chronic Obstructive Lung Disease; CCT = Clinical controlled trial; COACH = A Structured Lifestyle Intervention on Daily Physical Activity Level in COPD; COPD = chronic obstructive pulmonary disease; COPD-GRIP = Chronic Obstructive Pulmonary Disease – Guidance, Research on Illness Perception; CVD = Cardiovascular disease; ESC = Every Step Counts; FEV<sub>1</sub> =

**Table 6. Key Question 2 Results: Study Characteristics for Included Trials of Non-Pharmacologic Treatments**

forced expiratory volume in one second; FVC = Forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; MRC = Medical Research Council questionnaire; NR = not reported; PELICAN = Primary care EarLy Intervention for Copd mANagement; post-BD = post bronchodilator; PSM COPD = Patient self-management for chronic obstructive pulmonary disease; RADICALS = Review of Airway Dysfunction and Interdisciplinary Community-Based Care of Adult Long-Term Smokers; RCT = Randomized controlled trial; VA = Veterans Affairs.

**Table 7. Key Question 2 Results: Intervention Characteristics for Included Trials of Non-Pharmacologic Treatments**

Intervention type	Author, Year Study	Country	Intervention description	Delivery	Duration	Comparator	Adherence
Self-management	Bischoff, 2012 <sup>67</sup>	Netherlands	Tailored self-management education/support	2-4 in person sessions (1 hour) with nurse; 6 follow up phone calls	52 weeks	Usual care	NR
			Non-tailored self-management education/support*	1-4 routine monitoring nursing visits	52 weeks	Usual care	NR
	Jolly, 2018 <sup>69</sup> PSM COPD	United Kingdom	Telephone health coaching intervention to support self-management	4 nurse counseling telephone sessions (15-60 minutes) with tailored supportive materials	26 weeks	13-page informational leaflet on self-management	86.4% of scheduled calls were delivered and 75.4% of participants received all four calls
	Moy, 2016 <sup>86</sup> Taking Healthy Steps	United States	Pedometer plus educational and tracking website with personalized goals	Web/computer based	17 weeks with 35 week maintenance phase	Received pedometer and access to step count website	Step counts recorded by 77% of intervention group and 64% of control group
	Nyberg, 2019 <sup>73</sup>	Sweden	COPD self-management website (COPD Web)	Use of pedometer and interactive webpage	52 weeks	Received pedometer and information on importance of physical activity	95% of participants created an account and visited the site at least once (77% of participants were considered users)
	Voncken-Brewster, 2015 <sup>77</sup> MasterYour Breath	Netherlands	Web-based application providing computer-generated tailored feedback	Web/computer based	26 weeks	Usual care	36% of participants used application
	Wan, 2020 <sup>78</sup> ESC	United States	Pedometer plus educational and tracking website with personalized goals	Web/computer based	13 weeks	Received pedometer and access to step count website	Overall percentage of wear days: 85.8% (average 15.2 hours per day), >4 logins per month
	Weldam, 2017 <sup>79</sup> COPD-GRIP	Netherlands	Nurse consultations discussing individual patient illness, behavior, and action plan formation	3 in-person consultations (30 minutes); 4 hour educational session for nurses	6 weeks	Usual care	NR

**Table 7. Key Question 2 Results: Intervention Characteristics for Included Trials of Non-Pharmacologic Treatments**

Intervention type	Author, Year Study	Country	Intervention description	Delivery	Duration	Comparator	Adherence
Exercise only	Altenburg, 2015 <sup>66</sup> COACH	Netherlands	Customized lifestyle physical activity counselling program	5 individual 30-minute in-person counseling sessions by exercise counselors	12 weeks	Usual care	NR
Supervised exercise or pulmonary rehabilitation	Fastenau, 2020 <sup>68</sup>	Netherlands	Supervised exercise training	2 supervised group exercise sessions per week for 17 weeks (60-90 minutes)	17 weeks	Low intensity exercise program (30 minutes/once a week)	NR
	Liang, 2019 <sup>70</sup> RADICALS	Australia	Interdisciplinary, primary care-based model addressing smoking cessation, medication review and home-based pulmonary rehabilitation	In home pharmacist medication review and smoking cessation support (1.5 hours); 8-week home based pulmonary rehabilitation (one home visit and follow up phone calls)	8 weeks	Usual care plus informational booklet	Full intervention: 31% Partial intervention: 26% No intervention: 43%
	Roman, 2013 <sup>74</sup>	Spain	Small group pulmonary rehabilitation/education plus weekly maintenance program	3 (60-minute) sessions a week for 3 months; weekly sessions during months 4-12	52 weeks	Usual care	Attended 69.4% of the planned sessions during the first three months, and 58.3% of the planned sessions during the maintenance period
			Small group pulmonary rehabilitation/education	3 (60-minute) sessions a week for 3 months	2000 minutes over 13 weeks	Usual care	Attended 36.1% of the sessions during the three month period.
Clinician education only	Markun, 2018 <sup>71</sup> CAROL	Switzerland	COPD care bundle and provider education	Half day workshop for care providers, 3-hour refresher workshop after 6 months	provider training only, 26 weeks	Usual care	NR
	Zwar, 2016 <sup>80</sup> PELICAN	Australia	Provider education on team-based management of COPD	1-day (8 hour) nurse training on case-finding for COPD; 3-hour joint workshop for general practitioners and care team on care organization	provider education only, 1 day	1-day (8 hour) nurse training on case-finding for COPD; practice mailed a copy of COPD guidelines	15.3% of participants reported one or more visits to COPD care, 51.4% received one or more visits for any reason.

\* Referred to in trial as ‘routine monitoring’.

## Table 7. Key Question 2 Results: Intervention Characteristics for Included Trials of Non-Pharmacologic Treatments

**Abbreviations:** CAROL = Care in Chronic Obstructive Lung Disease; COACH = A Structured Lifestyle Intervention on Daily Physical Activity Level in COPD; COPD = chronic obstructive pulmonary disease; COPD-GRIP = Chronic Obstructive Pulmonary Disease – Guidance, Research on Illness Perception; ESC = Every Step Counts; NR = not reported; PELICAN = Primary care EarLy Intervention for Copd mANagement; PSM COPD = Patient self-management for chronic obstructive pulmonary disease; RADICALS = Review of Airway Dysfunction and Interdisciplinary Community-Based Care of Adult Long-Term Smokers.

**Table 8. Key Question 2 Results: Population Characteristics for Included Trials of Non-Pharmacologic Treatments**

Intervention type	Author, Year Study	Age, years (mean)	Female, %	Smoking status, %	Smoking history, pack-years (mean)	Number of exacerbations in preceding year	Lung function post-BD FEV <sub>1</sub> % predicted of normal (mean)	COPD Stage	HrQOL symptom score
Self-management	Bischoff, 2012 <sup>67</sup>	64.9	35	Current: 30	NR	Median: 0.5 to 1	65.4	NR	NR
	Jolly, 2018 <sup>69</sup> PSM COPD	70.4	37	Current: 23	NR	1 or more: 47%	71.7	1: 33% 2: 54% 3: 12% 4: <1%	SGRQ mean score: 28.7
	Moy, 2016 <sup>86</sup>	66.8	6	Current: 24	NR	NR	NR	mMRC 0-1: 69% mMRC 2-4: 31%	SGRQ mean score: 46
	Nyberg, 2019 <sup>73</sup>	68.0	43	Current: 19 Former: 71	30	NR	60.0	A: 53% B: 20% C: 8% D: 18%	EQ-5D mean score: 0.90
	Voncken-Brewster, 2015 <sup>77</sup> MasterYour Breath	57.6	52	Current: 34	NR	NR	NR*	NR	CCQ mean score: 1.0  MRC score: 0: 27.5%, 1: 40.1%, 2: 24.4%, 3+: 8%
	Wan, 2020 <sup>78</sup> ESC	68.6	2	Current: 37 Former: 63	61.5	Mean in previous year: 0.35	62.6	NR	SGRQ mean score: 33.5
	Weldam, 2017 <sup>79</sup> COPD-GRIP	67.0	55	Current: 30	NR	NR	60.6	1: 9% 2: 62% 3: 21% 4: 7%†	MRC mean score: 2.1

**Table 8. Key Question 2 Results: Population Characteristics for Included Trials of Non-Pharmacologic Treatments**

Intervention type	Author, Year Study	Age, years (mean)	Female, %	Smoking status, %	Smoking history, pack-years (mean)	Number of exacerbations in preceding year	Lung function post-BD FEV <sub>1</sub> % predicted of normal (mean)	COPD Stage	HrQOL symptom score
Exercise only	Altenburg, 2015 <sup>66</sup> COACH	65 <sup>‡</sup>	33	NR	30 <sup>‡</sup>	NR	78 <sup>‡</sup>	1: 46% 2: 48% 3: 6% 4: 0%	CRQ total mean: 117; CCQ total mean: 0.75
Supervised exercise or pulmonary rehabilitation	Fastenau, 2020 <sup>68</sup>	62.5	51	Current: 38 Former: 54	NR	NR	74.2	1: 27% 2: 73%	CCQ total score mean: 1.7
	Liang, 2019 <sup>70</sup> RADICALS	64.5	39	Current: 61	NR	NR	70.0	Mild: 70% Moderate: 21% Severe: 9%	NR
	Roman, 2013 <sup>74</sup>	64.2	18	Current: 34 Former: 62		39% <sup>§</sup>	60.3	2: 100%	NR
Clinician education only	Markun, 2018 <sup>71</sup> CAROL	67.5	41	Current: 56 Former: 44	44.5	1 or more: 34%	67.3	A: 59% B: 10% C: 19% D: 12%	CAT mean score: 10.6
	Zwar, 2016 <sup>80</sup> PELICAN	66.0	40	Current: 31 Former: 69	NR	NR	74.6	1: 21% 2: 42% 3: 6% 4: <1% <sup>  </sup>	SGQR mean score: 19.5; CAT: 10.2

\*Diagnosed with COPD: 21.7%, increased risk for COPD 78.3%

<sup>†</sup> 78 patients (31%) that a clinician assigned a diagnosis of COPD were found to not meet criteria for COPD (FEV<sub>1</sub>/FVC not <0.7) upon further assessment

<sup>‡</sup> Median

<sup>§</sup> 39 % with physician visit for exacerbation and 18% with hospitalization

<sup>||</sup> 78 patients (31%) that a clinician assigned a diagnosis of COPD were found to not meet criteria for COPD (FEV<sub>1</sub>/FVC not <0.7) upon further assessment

**Abbreviations:** CAT= COPD Assessment Test; CAROL = Care in Chronic Obstructive Lung Disease; CCQ = Clinical COPD Questionnaire; COACH = A Structured Lifestyle Intervention on Daily Physical Activity Level in COPD; COPD = chronic obstructive pulmonary disease; COPD-GRIP = Chronic Obstructive Pulmonary Disease – Guidance, Research on Illness Perception; CRQ = Chronic Respiratory Disease Questionnaire; EQ-5D = EuroQOL-5 Dimension Questionnaire; ESC = Every Step Counts; FEV<sub>1</sub> = forced expiratory volume in one second; HRQoL = Health Related Quality of Life; MRC = Medical Research Counsel questionnaire; NR = not reported; PELICAN = Primary care

**Table 8. Key Question 2 Results: Population Characteristics for Included Trials of Non-Pharmacologic Treatments**

EarLy Intervention for Copd mANagement; post-BD = post bronchodilator; PSM COPD = Patient self-management for chronic obstructive pulmonary disease; RADICALS = Review of Airway Dysfunction and Interdisciplinary Community-Based Care of Adult Long-Term Smokers; SGRQ = St George's Respiratory Questionnaire



**Table 9. Key Question 2 Results: Outcomes for Included RCTs of Pharmacologic Treatment**

Drug Class	Study, year	Treatment Comparison	Followup	Outcome	N analyzed	IG Events*	CG Events*	IG vs. CG
ICS	SUMMIT Vestbo, 2016 <sup>76</sup> Crim, 2017 <sup>83</sup>	Fluticasone furoate vs. placebo	1.8 years (Median)	All-cause mortality	8246	251/4135 (6.1%)	275/4111 (6.7%)	HR: 0.91 (95% CI, 0.77 to 1.08)
				Annual rate of moderate/severe exacerbations	8246	0.31	0.35	Percent reduction: 12% (95% CI, 4% to 19%)
				Annual rate of hospitalized exacerbation	8246	0.06	0.07	Percent reduction: 18% (95% CI, 3% to 31%)
				Composite CVD endpoint†	8246	161/4135 (3.9%)	173/4111 (4.2%)	HR: 0.90 (95% CI, 0.73 to 1.11)
LABA	PINNACLE Martinez, 2020 <sup>72</sup> SUMMIT Vestbo, 2016 <sup>76</sup> Crim, 2017 <sup>83</sup>	Formoterol fumarate vs. placebo Vilanterol vs. placebo	24 weeks 1.8 years (Median)	All-cause mortality	GOLD A: 318	1/205 (0.5%)	0/113 (0%)	NR
				All-cause mortality	8229	265/4118 (6.4%)	275/4111 (6.7%)	HR: 0.96 (95% CI, 0.81 to 1.14)
				Annual rate of moderate/severe exacerbations	8229	0.31	0.35	Percent reduction: 10% (95% CI, 2% to 18%)
				Annual rate of hospitalized exacerbation	8229	0.06	0.07	Percent reduction: 20% (95% CI, 5% to 32%)
LABA/ ICS	SUMMIT Vestbo, 2016 <sup>76</sup> Crim, 2017 <sup>83</sup>	Fluticasone furoate/vilanterol vs. placebo	1.8 years (Median)	All-cause mortality	8232	246/4121 (6.0%)	275/4111 (6.7%)	HR: 0.88 (95% CI, 0.74 to 1.04)
				Annual rate of moderate/severe exacerbations	8232	0.25	0.35	Percent reduction: 29% (95% CI, 22% to 35%)
				Annual rate of hospitalized exacerbation	8232	0.05	0.07	Percent reduction: 27% (95% CI, 13% to 39%)
				Composite CVD endpoint†	8232	174/4121 (4.2%)	173/4111 (4.2%)	HR: 0.93 (95% CI, 0.75 to 1.14)
LAMA	UPLIFT Decramer, 2009 <sup>87</sup> Tashkin, 2012 <sup>88</sup> Tashkin,	Tiotropium bromide vs. placebo	48 months	Clinically important deterioration‡	Stage II: 2,603	1053/1310 (80.4%)	1122/1293 (86.8%)	HR: 0.70 (95% CI, 0.65, 0.77)
				Exacerbations§	Stage II: 2,739	824/1384 (59.5%)	882/1355 (65.1%)	HR: 0.82 (95% CI, 0.75 to 0.90)

**Table 9. Key Question 2 Results: Outcomes for Included RCTs of Pharmacologic Treatment**

Drug Class	Study, year	Treatment Comparison	Followup	Outcome	N analyzed	IG Events*	CG Events*	IG vs. CG	
	2008 <sup>75</sup> Rabe, 2020 <sup>84</sup> Halpin, 2015 <sup>85</sup>				FEV <sub>1</sub> ≥60% : NR (1210 randomized)	NR (56%)	NR (62%)	HR: 0.83 (95% CI, 0.71 to 0.96)	
					GOLD category A: 357	91/188 (48.4%)	92/169 (54.4%)	RR: 0.64 (95% CI, 0.47 to 0.89) HR: 0.77 (95% CI, 0.58 to 1.03) <sup>†</sup>	
					Clinically meaningful deterioration in SGRQ <sup>¶</sup>	Stage II: 2,603	487/1310 (37.2%)	594/1293 (45.9%)	HR: 0.71 (0.63, 0.80)
					FEV <sub>1</sub> ≥60% : NR (1210 randomized)	NR (52%)	NR (44%)	P<0.05	
	PINNACLE Martinez, 2020 <sup>72</sup>	Glycopyrrolate vs. placebo	24 weeks	All-cause mortality	GOLD A: 308	0/195 (0%)	0/113 (0%)	NR	
LAMA/LABA	PINNACLE Martinez, 2020 <sup>72</sup>	Glycopyrrolate/formoterol fumarate vs. placebo	24 weeks	All-cause mortality	GOLD A: 330	0/217 (0%)	0/113 (0%)	NR	

\* Number of events or event rate

† Includes MI, unstable angina, stroke, TIA, sudden death, procedural death, other cardiovascular death

‡ SGRQ increase ≥4 units, trough FEV<sub>1</sub> decline ≥100mL, moderate/severe exacerbation

§ Increase/new onset >1 respiratory symptom for ≥ 3 days requiring antibiotic and/or systemic steroid

|| Time to first exacerbation

¶ SGRQ increase ≥4 units

**Abbreviations:** CG = control group; CI = confidence interval; CVD = cardiovascular disease; FEV<sub>1</sub>= forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; HR = hazard ratio; IG = intervention group; LABA = long acting beta agonist; LAMA = long acting muscarinic antagonist; µg = microgram; N = number; NR = not reported; SUMMIT = study to understand mortality and morbidity in COPD; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; Vs = versus

**Table 10. Key Question 2 Results: Exacerbation and Hospitalization Outcomes for Included Non-Pharmacologic Trials**

Intervention type	Author, Year Study	Treatment comparison	Outcome	Followup	N analyzed	IG Events	CG Events	IG vs. CG
Self-management	Bischoff, 2012 <sup>67</sup>	Tailored self-management intervention vs. usual care	Exacerbation*	52 weeks	101	Rate per patient: 2.83	Rate per patient: 2.73	RR: 1.10 (95% CI, 0.86 to 1.40)
				Weeks 52-104	101	Rate per patient: 2.45	Rate per patient: 2.17	RR: 1.16 (95% CI, 0.81 to 1.67)
		Non-tailored self-management intervention vs. usual care	Exacerbation*	52 weeks	103	Rate per patient: 3.25	Rate per patient: 2.73	RR: 1.25 (95% CI, 0.98 to 1.58)
				Weeks 52-104	103	Rate per patient: 2.38	Rate per patient: 2.17	RR: 1.15 (95% CI, 0.80 to 1.65)
	Jolly, 2018 <sup>69</sup> PSM COPD	Phone-based self-management intervention vs. printed information	Hospital admissions	26 weeks <sup>†</sup>	531	Mean (SD): 0.07 (0.3)	Mean (SD): 0.06 (0.3)	IRR: 0.86 (95% CI, 0.45 to 1.62), p=0.64
				52 weeks <sup>‡</sup>	516	Mean (SD): 0.06 (0.3)	Mean (SD): 0.06 (0.3)	IRR: 0.90 (95% CI, 0.39 to 2.09), p=0.81
	Moy, 2016 <sup>86</sup> Taking Healthy Steps	Web-based exercise intervention vs. pedometer only	Exacerbation or pneumonia	52 weeks	328	35/154 (22.7%)	15/84 (18%)	OR: 1.4 (95% CI, 0.7 to 2.8), p=0.33
			Hospitalization	52 weeks	328	36/154 (23.4%)	14/84 (17%)	OR: 1.6 (95% CI, 0.8 to 3.2), p=0.19
			Emergency room visit	52 weeks	328	46/154 (29.9%)	20/84 (24%)	OR: 1.4 (95% CI, 0.8 to 2.6), p=0.27
	Wan, 2020 <sup>78</sup> ESC	Web-based exercise intervention vs. pedometer only	Acute exacerbation <sup>§</sup>	65 weeks	109	NR	NR	RR: 0.51 (0.31 to 0.85) <sup>¶</sup>
Supervised-exercise or pulmonary rehabilitation	Roman, 2013 <sup>74</sup>	PR with maintenance program vs. usual care	Hospitalized for exacerbation	52 weeks	43	3/24 (12.5%)	3/19 (15.8%)	NS
			Primary care visit for exacerbation	52 weeks	43	7/24 (30.3%)	9/19 (42.8%)	NS
		PR vs. usual care	Hospitalized for exacerbation	52 weeks	41	5/22 (22.7%)	3/19 (15.8%)	NS
			Primary care visit for exacerbation	52 weeks	41	7/22 (35.0%)	9/19 (42.8%)	NS

\* Change for at least two consecutive days in either two or more major symptoms (dyspnea, sputum purulence, sputum amount) or any one major symptom plus at least one minor symptom (colds, wheeze, sore throat, cough)

<sup>†</sup> While overall admissions were not significant, intervention participants reported lower doctor and pharmacist consultations, but higher all cause emergency department visits

<sup>‡</sup> No differences across any utilization measure

<sup>§</sup> New or increased respiratory symptoms with  $\geq 2$  the following criteria: increased cough, sputum, wheezing, dyspnea, or chest tightness for  $\geq 3$  days requiring antibiotics or new/increased systemic steroid use

<sup>¶</sup> Favors intervention group

**Table 10. Key Question 2 Results: Exacerbation and Hospitalization Outcomes for Included Non-Pharmacologic Trials**

**Abbreviations:** CG = control group; CI = confidence interval; ESC = Every Step Counts; IG = intervention group; IRR = incidence rate ratio; N = number; NR = not reported; NS = not significant; OR = odds ratio; PR = pulmonary rehabilitation; PSM COPD = Patient self-management for chronic obstructive pulmonary disease; RR = rate ratio; SD = standard deviation; Vs = versus

**Table 11. Key Question 2 Results: Quality of Life Outcomes for Included Trials of Non-Pharmacologic Treatment**

Intervention type	Author, Year Study	Treatment comparison	Followup	Outcome measure	N analyzed	IG: % with MCID	CG: % with MCID	Effect estimate*
Self-management	Bischoff, 2012 <sup>67</sup>	Tailored self-management intervention vs. usual care	104 weeks	CRQ	110	NR	NR	-0.22 (95% CI, -0.49 to 0.042)
		Non-tailored self-management intervention vs. usual care	104 weeks	CRQ	110	13/46 (28%)	8/44 (18%)	OR (MCID): 1.44 (95% CI, 0.61 to 3.38) Difference in change: 0.16 (95% CI, -0.11 to 0.42)
	Jolly, 2018 <sup>69</sup> PSM COPD	Phone-based self-management intervention vs. printed information	26 weeks	EQ-5D	516	NR	NR	0.01 (95% CI, -0.01 to 0.03), p=0.30
				SGRQ	459	NR	NR	-0.3 (95% CI, -2.3 to 1.7), p=0.76
			52 weeks	EQ-5D	505	NR	NR	0.01 (95% CI, -0.01 to 0.03), p=0.38
				SGRQ	473	NR	NR	-1.3 (95% CI, -3.6 to 0.9), p=0.23
	Moy, 2016 <sup>86</sup> Taking Healthy Steps	Web-based exercise intervention vs. pedometer only	52 weeks	SGRQ	238	NR	NR	1.1 (95% CI, -2.2 to 4.5), p=0.50
	Nyberg, 2019 <sup>73</sup>	Web-based self-management intervention vs. pedometer	52 weeks	CAT	83	NR	NR	Beta-coefficient: -1.1 (95% CI, -2.2 to 4.3), p=0.521
				EQ-5D	83	NR	NR	Beta-coefficient: 0.02 (95% CI, -0.03 to 0.07), p=0.980
	Voncken-Brewster, 2015 <sup>77</sup> MasterYourBreath	Web-based self-management intervention vs. usual care	26 weeks	CCQ	1307	NR	NR	Beta-coefficient: -0.03 (95% CI, -0.07 to 0.01), p=0.134
Wan, 2020 <sup>78</sup> ESC	Web-based exercise intervention vs. pedometer only	52 weeks	SGRQ	109	NR	NR	NS	
Weldam, 2017 COPD-GRIP	In-person self-management intervention vs usual care	39 weeks	CCQ	199	16/100 (15.7%)	13/99 (12.9%)	OR (MCID): NS Difference in change: 0.04 (95% CI, -0.09 to 0.17), p=0.197	
Exercise only	Altenburg, 2015 <sup>66</sup> COACH	Lifestyle/exercise counseling vs usual care	65 weeks	CCQ	38	NR	NR	p=0.536
				CRQ	38	NR	NR	p=0.278
Supervised exercise or pulmonary rehabilitation	Fastenau, 2020 <sup>68</sup>	Supervised exercise vs. low intensity exercise	26 weeks	CCQ	67	NR	NR	-0.09 (95% CI, -0.4 to 0.2), p=0.549
	Liang, 2019 <sup>70</sup> RADICALS	Lifestyle counseling plus home PR vs. usual care	26 weeks	CAT	208	NR	NR	0.66 (95% CI, -1.98 to 3.30) p=0.61
				SGRQ	204	NR	NR	2.45 (95% CI, -0.89 to 5.79), p=0.15
			52 weeks	CAT	189	NR	NR	0.86 (95% CI, -2.02 to 3.74) p=0.55
				SGRQ	185	47/105 (44.8%)	38/90 (42.2%)	2.21 (95% CI, -2.86 to 7.28), p=0.38
Roman, 2013 <sup>74</sup>	PR with maintenance program vs. usual care	52 weeks	CRQ	36	NR	NR	NS for any subscale (total score NR)	

**Table 11. Key Question 2 Results: Quality of Life Outcomes for Included Trials of Non-Pharmacologic Treatment**

Intervention type	Author, Year Study	Treatment comparison	Followup	Outcome measure	N analyzed	IG: % with MCID	CG: % with MCID	Effect estimate*
		PR vs. usual care	52 weeks	CRQ	31	NR	NR	NS for any subscale (total score NR)
Clinician education only	Markun, 2018 <sup>71</sup> CAROL	Clinician training vs. usual care	52 weeks	CAT	216	NR	NR	-1.1 (95% CI, -3.3 to 1.1), p=0.32
	Zwar, 2016 <sup>80</sup> PELICAN	Clinician training vs. written information	52 weeks	CAT	222	NR	NR	LSM change: -0.20 (95% CI, -1.53 to 1.12), 0.73
				SGRQ	222	NR	NR	LSM change: -0.21 (95% CI, -2.55 to 2.14), 0.86

\*Mean difference unless otherwise noted

**Abbreviations:** CAROL = Care in Chronic Obstructive Lung Disease; CAT= COPD Assessment Test; CCQ = Clinical COPD Questionnaire; CG = control group; CI = confidence interval; COACH = A Structured Lifestyle Intervention on Daily Physical Activity Level in COPD; CRQ = Chronic Respiratory Disease Questionnaire; EQ-5D = EuroQOL-5 Dimension Questionnaire; IG = intervention group; LSM = least squares mean; MCID = minimal clinically important difference; mMRC = modified Medical Research Counsel questionnaire; MRC = Medical Research Counsel questionnaire N = number; NR = not reported; NS = not significant; OR = odds ratio; PELICAN = Primary care EarLy Intervention for Copd mANagement; PR = pulmonary rehabilitation; PSM COPD = Patient self-management for chronic obstructive pulmonary disease; RADICALS = Review of Airway Dysfunction and Interdisciplinary Community-Based Care of Adult Long-Term Smokers; SGRQ = St George's Respiratory Questionnaire

**Table 12. Key Question 2 Results: Dyspnea Outcomes for Included Trials of Non-Pharmacologic Treatment**

Intervention type	Author, Year Study	Treatment comparison	Followup	Outcome measure	N analyzed	IG: % with MCID	CG: % with MCID	Effect estimate*
Self-management	Bischoff, 2012 <sup>67</sup>	Tailored self-management education/support vs. usual care	26 weeks	CRQ-Dyspnea domain	110	NR	NR	-0.098 (95% CI: -0.47 to 0.28)
			104 weeks	CRQ-Dyspnea domain	110	NR	NR	-0.16 (95% CI: -0.54 to 2.1)
		Non-tailored self-management education/support vs. usual care	26 weeks	CRQ-Dyspnea domain	110	NR	NR	0.12 (95% CI: -0.26 to 0.49)
			104 weeks	CRQ-Dyspnea domain	110	NR	NR	0.40 (95% CI: 0.041 to 0.78); p=0.042
	Jolly, 2018 <sup>69</sup> PSM COPD	Phone-based self-management intervention vs. printed information	26 weeks	MRC	495	NR	NR	OR: 0.8 (95% CI: 0.6 to 1.2); p=0.39
			52 weeks	MRC	495	NR	NR	OR: 1.1 (95% CI: 0.7 to 1.5); p=0.79
	Nyberg, 2019 <sup>73</sup>	Web-based self-management intervention vs. pedometer	52 weeks	mMRC	83	NR	NR	Beta coefficient: -0.1 (95% CI: -0.4 to 0.3); p=0.709
	Voncken-Brewster, 2015 <sup>77</sup> MasterYourBreath	Web-based self-management intervention vs. usual care	26 weeks	MRC	1,307	NR	NR	OR: 1.28 (95% CI: 0.92 to 1.79); p=0.149
Weldam, 2017 <sup>79</sup> COPD-GRIP	In-person self-management intervention vs usual care	39 weeks	CRQ- Dyspnea domain	163	NR	NR	0.16 (95% CI: -0.13 to 0.04); p=0.162	
Supervised exercise or pulmonary rehabilitation	Fastenau, 2020 <sup>68</sup>	Supervised exercise vs. low intensity exercise	26 weeks	MRC	67	NR	NR	-0.03 (95% CI: -0.3 to 0.3); p=0.867
	Liang, 2019 <sup>70</sup> RADICALS	Lifestyle counseling plus home PR vs. usual care	26 weeks	mMRC	208	NR	NR	Any improvement from baseline: IG 23.7%, CG: 17.0%, p=0.31
			52 weeks	mMRC	190	NR	NR	Any improvement from baseline: IG 21.2%, CG: 18.2%, p=0.74
	Roman, 2013 <sup>74</sup>	PR with maintenance program vs. usual care	52 weeks	CRQ-Dyspnea domain	49	NR	NR	Mean difference in change: 0.1 (95% CI: -0.5 to 0.8)
		PR vs. usual care		CRQ-Dyspnea domain	31	NR	NR	Mean difference in change: 0.5 (95% CI: -0.2 to 1.1)

\*mean difference unless otherwise noted

**Abbreviations:** CG = control group; CI = confidence interval; CRQ = Chronic Respiratory Disease Questionnaire; IG = intervention group; MCID = minimal clinically important difference; mMRC = Modified Medical Research Counsel questionnaire; MRC = Medical Research Counsel questionnaire; N = number; NR = not reported; OR = odds ratio; PSM

**Table 12. Key Question 2 Results: Dyspnea Outcomes for Included Trials of Non-Pharmacologic Treatment**

COPD = Patient self-management for chronic obstructive pulmonary disease; PR= pulmonary rehabilitation; RADICALS = Review of Airway Dysfunction and Interdisciplinary Community-Based Care of Adult Long-Term Smokers



**Table 13. Key Question 2 Results: Exercise and Physical Functioning Outcomes for Included Trials of Non-Pharmacologic Treatment**

Intervention type	Author, Year Study	Treatment comparison	Followup	Outcome measure	N analyzed	IG vs. CG
Self-management	Jolly, 2018 <sup>69</sup> PSM COPD	Phone-based self-management intervention vs. printed information	26 weeks	MET minutes a week (IPAQ)	506	Total self-reported physical activity, walking, moderate, and vigorous intensity activity were all significantly higher in the intervention arm at 6 months
			52 weeks	MET minutes a week (IPAQ)	482	NS
	Moy, 2016 <sup>86</sup> Taking Healthy Steps	Web-based exercise intervention vs. pedometer only	52 weeks	Average daily step count	328	NS
	Nyberg, 2019 <sup>73</sup>	Web-based self-management intervention vs. pedometer	52 weeks	Physical activity (self-reported)	83	NS
	Voncken-Brewster, 2015 <sup>77</sup> MasterYourBreath	Web-based self-management intervention vs. usual care	26 weeks	MET minutes a week (IPAQ-SF)	1,307	NS
	Wan, 2020 <sup>78</sup> ESC	Web-based exercise intervention vs. pedometer only	26 weeks	Average daily step count	87	NS
52 weeks			Average daily step count	75	NS	
Exercise only	Altenburg, 2015 <sup>66</sup> COACH	Lifestyle/exercise counseling vs usual care	65 weeks	6MWD	38	Mean difference: NR, p=0.313 <sup>†</sup>
Supervised exercise or pulmonary rehabilitation	Fastenau, 2020 <sup>68</sup>	Supervised exercise vs. low intensity exercise	26 weeks	6MWD	67	Mean difference: 20.1 (95% CI: -6.5 to 46.7) <sup>†</sup>
	Roman, 2013 <sup>74</sup>	PR with maintenance program vs. usual care	52 weeks	6MWD	36	Mean difference in change: -13.5 (95%: -55.5 to 28.5)
		PR vs. usual care	52 weeks	6MWD	31	Mean difference in change: -12.9 (95%: -56.7 to 30.7)

\* Daily steps/daily physical activity (measured via pedometer) were also not significantly different between groups

<sup>†</sup>Reports other physical activity outcomes, none were significant other than handgrip strength.

**Abbreviations:** 6MWD= 6 minute walking distance during the 6 minute walk test (6MWT); CI = confidence interval; ESC = Every step counts; COACH = A Structured Lifestyle Intervention on Daily Physical Activity Level in COPD; IG = intervention group; IPAQ = International Physical Activity Questionnaire; IPAQ-SF = International Physical Activity Questionnaire short form; MET = metabolic equivalent of task; N = number; PSM COPD = Patient self-management for chronic obstructive pulmonary disease; vs = versus

**Table 14. Key Question 2 Results: Smoking Cessation and Vaccination Outcomes for Included Trials of Non-Pharmacologic Treatment**

Intervention type	Author, Year Study	Intervention comparison	Followup	Outcome	N analyzed	IG	CG	IG vs. CG
Self-management	Jolly, 2018 <sup>69</sup> PSM COPD	Phone-based self-management intervention vs. printed information	26 weeks	Smoking cessation	114	14/64 (22%)	9/50 (18%)	P=0.60
			52 weeks	Smoking cessation	106	7/54 (13%)	13/52 (25%)	P=0.11
	Voncken-Brewster, 2015 <sup>77</sup> MasterYourBreath	Web-based self-management intervention vs. usual care	26 weeks	7-day point prevalence abstinence	341	NR	NR	OR=1.06 (95% CI: 0.43 to 2.66)
				24-hour point prevalence of abstinence	341	NR	NR	OR=0.72 (95% CI: 0.33 to 1.59)
				Continued abstinence*	341	NR	NR	OR=0.98 (95% CI: 0.37 to 2.63)
				Prolonged abstinence <sup>†</sup>	341	NR	NR	OR=0.86 (95% CI: 0.33 to 2.25)
				Tobacco consumption	341	NR	NR	Beta-coefficient =0.11 (95% CI: -1.61 to 1.84)
				Intention to quit smoking	341	NR	NR	Beta-coefficient =-0.03 (95% CI: -0.32 to 0.26)
Number of quit attempts	341	NR	NR	Beta-coefficient=-0.38 (95% CI: -1.11 to 0.36)				
Clinician education only	Zwar, 2016 <sup>80</sup> PELICAN	Clinician training vs. written information	52 weeks	Number of current smokers	222	28/126 (22%)	25/96 (26%)	OR: 0.92 (95% CI: 0.44 to 1.91)
				Vaccinated for influenza	222	91/126 (73%)	54/96 (57%)	OR: 2.31 (95% CI: 1.06 to 5.03)
				Vaccinated for pneumococcus	222	53/126 (48%)	36/96 (38%)	OR: 1.54 (95% CI: 0.86 to 2.71)

\* Not smoked at all since last quit date

† Not smoked in two weeks since last quit date)

‡ Reports Ex-SRES: Exercise self efficacy (NS) and step counts (NS)

§ Also reports daily steps/daily physical activity (measured via pedometer) were also not significantly different between groups

**Abbreviations:** CG control group; CI = confidence interval; IG = intervention group; N = number; NR = not reported; OR = odds ratio; PELICAN = Primary care EarLy Intervention for Copd mANagement; PSM COPD = Patient self-management for chronic obstructive pulmonary disease; vs. = versus.

**Table 15. Key Question 3 Results: Adverse Events for Included RCTs of Pharmacologic Treatment**

Drug Class	Study, year	Treatment Comparison	Followup	Outcome	N analyzed	IG Events	CG Events	IG vs. CG
ICS	SUMMIT Vestbo, 2016 <sup>76</sup> Crim, 2017 <sup>83</sup>	Fluticasone furoate vs. placebo	1.8 years (median)	Adverse events	8288	2820/4157 (68%)	2782/4131 (67%)	NR
				Serious adverse events	8288	929/4157 (22%)	918/4131 (22%)	NR
				Fatal adverse events	8288	183/4157 (4%)	192/4131 (5%)	NR
				Medication discontinuation due to adverse event	8288	367/4157 (9%)	397/4131 (10%)	NR
				Pneumonia	8288	228/4157 (5.5%)	214/4131 (5.2%)	HR: 1.035 (95% CI, 0.859 to 1.247), p=0.716
				Severe pneumonia	8288	146/4157 (3.5%)	127/4131 (3.1%)	HR: 1.17 (95% CI, 0.880 to 1.416), p=0.364
				Fatal pneumonia	8288	10/4157 (0.2%)	9/4131 (0/2%)	HR: 1.079 (95% CI, 0.438 to 2.657), p=0.868
LABA	PINNACLE Martinez, 2020 <sup>72</sup>	Formoterol fumarate vs. placebo	24 weeks	Serious adverse events	318	15/205 (7.3%)	7/113 (6.2%)	NR
				Serious adverse events related to study treatment*	318	0/205 (0%)	1/113 (0.9%)	NR
				Treatment related adverse events leading to early discontinuation	318	7/205 (3.4%)	8/113 (7.1%)	NR
LABA/ ICS	SUMMIT Vestbo, 2016 <sup>76</sup> Crim, 2017 <sup>83</sup>	Vilanterol vs. placebo	1.8 years (median)	Adverse events	8271	2809/4140 (68%)	2782/4131 (67%)	NR
				Serious adverse events	8271	972/4140 (23%)	918/4131 (22%)	NR
				Fatal adverse events	8271	198/4140 (4%)	192/4131 (5%)	NR
				Medication discontinuation due to adverse event	8271	370/4140 (9%)	397/4131 (10%)	NR
				Pneumonia	8271	163/4140 (3.9%)	214/4131 (5.2%)	HR: 0.722 (95% CI, 0.589 to 0.886), p=0.002
				Severe pneumonia	8271	104/4140 (2.5%)	127/4131 (3.1%)	HR: 0.778 (95% CI, 0.600 to 1.008), p=0.057
				Fatal pneumonia	8271	6/4140 (0.1%)	9/4131 (0/2%)	HR: 0.632 (95% CI, 0.225 to 1.777), p=0.384
LABA/ ICS	SUMMIT Vestbo,	Fluticasone furoate/vilanterol	1.8 years (median)	Adverse events	8271	2780/4140 (67%)	2782/4131 (67%)	NR

**Table 15. Key Question 3 Results: Adverse Events for Included RCTs of Pharmacologic Treatment**

Drug Class	Study, year	Treatment Comparison	Followup	Outcome	N analyzed	IG Events	CG Events	IG vs. CG
	2016 <sup>76</sup> Crim, 2017 <sup>83</sup>	vs. placebo		Serious adverse events	8271	961/4140 (23%)	918/4131 (22%)	NR
				Fatal adverse events	8271	182/4140 (4%)	192/4131 (5%)	NR
				Medication discontinuation due to adverse event	8271	342/4140 (8%)	397/4131 (10%)	NR
				Pneumonia	8271	237/4140 (5.7%)	214/4131 (5.2%)	HR: 1.038 (95% CI, 0.863 to 1.249), p=0.693
				Severe pneumonia	8271	140/4140 (3.4%)	127/4131 (3.1%)	HR: 1.022 (95% CI, 0.804 to 1.300), p=0.858
				Fatal pneumonia	8271	13/4140 (0.3%)	9/4131 (0.2%)	HR: 1.330 (95% CI, 0.567 to 3.117), p=0.512
LAMA	UPLIFT Decramer 2009 <sup>87</sup> Tashkin, 2012 <sup>88</sup> Tashkin, 2008 <sup>75</sup> Rabe, 2020 <sup>84</sup> Halpin, 2015 <sup>85</sup>	Tiotropium bromide vs. placebo	48 months	Adverse events leading to discontinuation	Stage II subset: 2,739	235/1384 (17.0%)	241/1355 (17.8%)	NR
					FEV <sub>1</sub> ≥60% subset: 1210	98/632 (15.5%)	88/578 (15.2%)	NR
				Fatal Adverse event	Category A: 357	13/188 (6.9%)	11/169 (6.5%)	RR: 1.03 (95% CI, 0.46 to 2.29)
				Fatal major cardiac events	Category A: 357	4/188 (2.1%)	12/169 (7.1%)	RR: 0.79 (95% CI, 0.35 to 1.78)
				Major adverse cardiac event	Category A: 357	11/188 (5.9%)	3/169 (1.8%)	RR: 1.16 (95% CI, 0.26 to 5.18)
	PINNACLE Martinez, 2020 <sup>72</sup>	Glycopyrrolate vs. placebo	24 weeks	Serious adverse events	308	7/195 (3.6%)	7/113 (6.2%)	NR
				Serious adverse events related to study treatment	308	3/195 (1.5%)	1/113 (0.9%)	NR
				Treatment related adverse events leading to early discontinuation	308	9/195 (4.6%)	8/113 (7.1%)	NR
LAMA/LABA	PINNACLE Martinez, 2020 <sup>72</sup>	Glycopyrrolate/formoterol fumarate vs. placebo	24 weeks	Serious adverse events	330	16/217 (7.4%)	7/113 (6.2%)	NR
				Serious adverse events related to study treatment	330	4/217 (1.8%)	1/113 (0.9%)	NR
				Treatment related adverse events leading to early discontinuation	330	12/217 (5.5%)	8/113 (7.1%)	NR

\* Adjudicated by investigator prior to unblinding

**Table 15. Key Question 3 Results: Adverse Events for Included RCTs of Pharmacologic Treatment**

**Abbreviations:** CG = control group; CI = confidence interval; HR = hazard ratio; ICS = inhaled corticosteroids; IG = intervention group; LABA = long acting beta agonist; LAMA = long acting muscarinic antagonist; µg = microgram; N = number of participants; NR = not reported; RR = relative risk; SUMMIT = study to understand mortality and morbidity in COPD; UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium; vs = versus.

**Table 16. Key Question 3 Results: Adverse Events for Included Observational Studies of Pharmacologic Treatment**

Drug Class	Study, year Quality	Study design Country, years	Population description	Outcome	N analyzed Follow-up	IG vs. CG
LABA or LAMA	Wang, 2018 <sup>82</sup>  Fair	Nested case-control Taiwan, 2007-2011	LABA-LAMA naïve patients; 71.4 years (mean); 31.1% female; mean FEV <sub>1</sub> NR	Risk of cardiovascular disease	N=37,719 cases; N=146,139 controls  Mean 2.0 years	LABA new use N=520 (1.4%) cases N=1186 (0.8%) controls Adjusted OR= 1.50 (95% CI: 1.35 to 1.67)
						LABA prevalent use N=962 (2.6%) cases N=3795 (2.6%) controls Adjusted OR=0.91 (95% CI: 0.85 to 0.98)
ICS	Price, 2019 <sup>81</sup>  Fair	Cohort UK, 1990-2015	Mean age 68-71 years; 38-41% female; 55-74% stage 1/2; 63-66% GOLD class A/B	Diabetes onset (ICS vs. LABA initiation)	N = 17,970 (Category A/B subset: N = 9,923)  Median 3.7-5.6 years	All patients HR=1.27 (95% CI, 1.07 to 1.50) Gold A/B HR=1.32(95% CI, 1.06 to 1.64)
				Diabetes progression (ICS vs. LABA initiation)	N = 804 (Category A/B subset: N = 492)  Median 3.7-5.6 years	All patients HR=1.04 (95% CI, 0.87 to 1.25) GOLD A/B HR=1.01 (95% CI, 0.80 to 1.28)
				Osteoporosis onset (ICS vs. LABA initiation)	N = 19,898 (Category A/B subset: N = 11,057)  Median 3.7-5.6 years	All patients HR=1.13 (95% CI, 0.93 to 1.39) GOLD A/B HR=1.06 (95% CI, 0.82 to 1.37)

**Abbreviations:** CG = control group; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV<sub>1</sub> = forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; ICS = inhaled corticosteroid; IG = intervention group; LABA = long-acting beta agonist; LAMA = long acting muscarinic antagonist; N = number; NR = not reported; OR = odds ratio; vs = versus.

**Table 17. Summary of Targeted Evidence Update in the Context of the Prior Systematic Review to Support the 2016 USPSTF Screening for COPD Recommendation\***

	<b>Evidence summary in 2016</b>	<b>New evidence findings</b>	<b>Limitations of new evidence</b>	<b>Consistency of new evidence with prior evidence findings</b>
KQ1: Effectiveness of screening	No trials evaluated the effectiveness of screening or active case finding for COPD on patient health outcomes (i.e., COPD morbidity, mortality, HRQoL).	No published or ongoing trials identified.	NA	NA
KQ2: Treatment benefits in screen relevant populations	Overall, the included treatment evidence (14 trials <sup>†</sup> ) for bronchodilators and ICS was largely limited to subgroup analyses, almost exclusively among individuals with moderate, and primarily the more severe end of moderate, COPD (e.g., FEV <sub>1</sub> 60% predicted). Even among these groups, the only consistent benefit observed was reduced COPD exacerbations with no consistent benefits in mortality, dyspnea, or HRQoL.	Based on 3 trials, LABA, LAMA, ICS or LABA/ICS can reduce COPD exacerbations in persons with moderate COPD. Based on subgroup analyses from one trial, LAMA (i.e., tiotropium) can reduce clinically important deterioration (composite outcome) in persons with moderate COPD and exacerbations in minimally symptomatic (i.e., GOLD category A) persons with moderate airflow obstruction.  Based on 13 trials, no consistent benefit for a range of non-pharmacologic interventions (i.e., self-management, exercise counseling, supervised exercise, pulmonary rehabilitation, clinician education) observed across multiple outcomes.	Subgroup analysis of LAMA in GOLD category A limited to 357 persons.  Non-pharmacologic intervention trials were generally small, had usual comparator groups in settings which may provide more care than typically received in the US, and/or had suboptimal uptake of the intervention, all of which may limit the ability to detect a true benefit.	Generally consistent for limited benefit of bronchodilators and ICS for reduction in exacerbation outcomes only in mainly persons with moderate COPD with unclear wider applicability to screen-detected persons with COPD.  Signal for benefit of tiotropium for COPD on exacerbations in minimally symptomatic persons who may be more representative of a screen-detected population despite moderate airflow obstruction.  New evidence for non-pharmacologic interventions with no consistent benefit across different outcomes.
KQ3: Treatment harms in screen relevant populations	Overall, limited data on serious harms reported in included treatment trials (8 trials) suggested no substantial serious adverse effects for most bronchodilators and ICS.	Based on 3 trials and 2 large observational studies, initiation of LAMA or LABA is associated with an increase in risk of serious cardiovascular events and treatment with ICS is associated with an increase in the risk of developing diabetes. Three self-management intervention trials did not demonstrate any serious harms.	Harms are not consistently reported in trials of pharmacologic and non-pharmacologic interventions. Treatment trials are limited in their ability to detect uncommon or longer-term harms.	Generally consistent for no serious harms from treatment trials, but large observational studies in screen-relevant populations suggest possible harms for LAMA or LABA initiation or use of ICS. Evidence, not limited to screen-relevant populations, suggest that LABA, but not LAMA, can increase risk of cardiovascular disease, and long-term ICS use may adversely affect bone health.
CQ: COPD diagnosis on recommend	Overall, the included evidence (5 studies) did not demonstrate a benefit for the incremental value of adding spirometry to smoking	Based on 3 included non-pharmacologic intervention trials and 1 additional comparative study looking at receipt of spirometry results (or 'lung age'), detection	Limited evidence with varying study designs evaluating the benefit of screening for COPD on	Generally consistent for no consistent benefit of spirometry or screening for COPD on smoking cessation. Benefits were only

**Table 17. Summary of Targeted Evidence Update in the Context of the Prior Systematic Review to Support the 2016 USPSTF Screening for COPD Recommendation\***

	<b>Evidence summary in 2016</b>	<b>New evidence findings</b>	<b>Limitations of new evidence</b>	<b>Consistency of new evidence with prior evidence findings</b>
er preventive services	cessation. And no studies evaluated spirometry or the incremental benefit of having a diagnosis of COPD on vaccination uptake.	of COPD did not increase smoking cessation. One trial evaluating clinician education demonstrated an increase in the uptake of influenza vaccination.	the uptake of preventive services.	observed in one trial that has not yet been reproduced. Still no comparative studies demonstrating the incremental benefit of spirometry or identification of COPD on uptake of recommended vaccinations or lung cancer screening.

\* Questions around the diagnostic accuracy and inaccuracy (harms) of questionnaires, spirometry and other screeners were not addressed in this review

† Two long-acting beta agonist (LABA) studies, one ICS-LABA combination study, five tiotropium studies (LAMA), and six ICS studies

**Abbreviations:** COPD = chronic obstructive pulmonary disease; FEV<sub>1</sub> = forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQoL = health related quality of life; ICS = inhaled corticosteroid; IG = intervention group; LABA = long-acting beta agonist; LAMA = long acting muscarinic antagonist; NA = not applicable



**Table 18. Contextual Question: RCTs Evaluating Spirometry or “Lung Age” on Smoking Cessation Outcomes**

Study, Year	Country	N Randomized	Population	Treatment Comparison	Followup	Smoking abstinence
Kotz, 2009 <sup>110, 128-130</sup>	Netherlands	296	Smokers aged 35-70 years; ≥1 respiratory symptom and mild or moderate COPD	Smoking cessation support with or without discussion of spirometry	52 weeks	Adjusted OR: 0.88 (95% CI, 0.38 to 2.03) <sup>*</sup>
McClure, 2009 <sup>111, 131, 132</sup>	US	542	Smokers aged ≥18 years	Smoking cessation support with spirometry results vs. smoking cessation support and “lung age” <sup>†</sup>	52 weeks	30-day abstinence: OR: 0.77 (95% CI NR); p=0.34 <sup>‡</sup> 7-day abstinence: OR: 0.86 (95% CI NR); p=0.38 <sup>‡</sup>
Parkes, 2008 <sup>112</sup>	UK	561	Smokers aged ≥35 years	Smoking cessation support with spirometry results vs. smoking cessation support and “lung age” <sup>§</sup>	52 weeks	Between group difference: 7.2% (95% CI: 2.2% to 12.1%) <sup>*</sup>
Risser, 1990 <sup>113</sup>	US	90	Smokers in VA Demonstration Project	Smoking cessation support with or without discussion of spirometry	52 weeks	IG: 20.0%, CG 6.7%, p=0.06 <sup>†</sup>
Ronaldson, 2018 <sup>115</sup>	UK	674	Smokers aged ≥35 years	Lung function testing and COPD case finding vs waitlist control	24 weeks	Adjusted OR: 1.00 (95% CI, 0.57 to 1.77) <sup>‡</sup>
Sippel, 1999 <sup>114</sup>	US	205	Smokers aged ≥18	Smoking cessation support with or without discussion of spirometry	39 weeks	Adjusted OR: 0.6 (95% CI, 0.2 to 1.4) <sup>‡</sup>

\* Biochemically validated smoking cessation

† Calculated using method Morris and Temple method<sup>133</sup>

‡ Self-reported smoking cessation

§ Men: Lung age= 2.87 x height (in inches) – (31.25 x observed FEV<sub>1</sub> (liters) - 39.375; Women: Lung age= 3.56 x height (in inches) – (40 x observed FEV<sub>1</sub> (liters) - 77.28

|| Self-reported smoking cessation- IG: 24.4%, CG: 11.1% (p=0.08)

**Abbreviations:** CI = confidence interval; COPD = chronic obstructive pulmonary disease; N = number; NR = not reported; OR = odds ratio; UK = United Kingdom; US = United States; VA = Veteran’s Affairs; VS = versus.

## Appendix A. Detailed Methods

### Literature search strategy

Key:

/ = MeSH subject heading

\$ = truncation

ti = word in title

ab = word in abstract

pt = publication type

\* = truncation

kw = keyword

AG = age

TX = all text

### **MEDLINE**

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 22, 2020>

Search Strategy:

- 
- 1 Pulmonary Disease, Chronic Obstructive/
  - 2 Bronchitis, Chronic/
  - 3 Lung Diseases, Obstructive/
  - 4 asthma-chronic obstructive pulmonary disease overlap syndrome/
  - 5 (chronic obstruct\$ or chronic airflow limitation\$ or obstructive lung or chronic bronchitis or COPD or COAD).ti.
  - 6 (chronic obstruct\$ or chronic airflow limitation\$ or obstructive lung or chronic bronchitis or COPD or COAD).ti,ab.
  - 7 limit 6 to ("in data review" or in process or publisher or "pubmed not medline")
  - 8 or/1-5,7
  - 9 Mass screening/
  - 10 Spirometry/
  - 11 Bronchspirometry/
  - 12 Respiratory Function Tests/
  - 13 screen\$.ti,ab.
  - 14 spiromet\$.ti,ab.
  - 15 bronchspiromet\$.ti,ab.
  - 16 ((respiratory or lung) adj2 function test\$.ti,ab.
  - 17 or/9-16
  - 18 8 and 17
  - 19 Pulmonary Disease, Chronic Obstructive/di [Diagnosis]
  - 20 Bronchitis, Chronic/di
  - 21 Lung Diseases, Obstructive/di
  - 22 or/18-21
  - 23 (clinical trial or adaptive clinical trial or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or equivalence trial or pragmatic clinical trial or Meta-Analysis).pt.
  - 24 clinical trials as topic/ or adaptive clinical trials as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or non-randomized controlled trials

## Appendix A. Detailed Methods

as topic/ or randomized controlled trials as topic/ or equivalence trials as topic/ or intention to treat analysis/ or pragmatic clinical trials as topic/ or meta-analysis as topic/  
25 control groups/ or double-blind method/ or single-blind method/ or random allocation/ or placebos/  
26 (randomized or randomised or placebo or randomly or phase iii or phase 3).ti,ab.  
27 (RCT or sham or dummy or single blind\$ or double blind\$ or allocated or allocation or triple blind\$ or treble blind\$).ti,ab.  
28 ((control\$ or clinical) adj3 (study or studies or trial\$ or group\$)).ti,ab.  
29 (Nonrandom\$ or non random\$ or non-random\$ or quasi-random\$ or quasirandom\$).ti,ab.  
30 ((open label or open-label) adj5 (study or studies or trial\$)).ti,ab.  
31 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial\$)).ti,ab.  
32 (pragmatic study or pragmatic studies).ti,ab.  
33 ((pragmatic or practical) adj3 trial\$).ti,ab.  
34 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial\$)).ti,ab.  
35 (metaanaly\$ or meta analy\$).ti,ab.  
36 or/23-35  
37 22 and 36  
38 limit 37 to (english language and yr="2015 -Current")  
39 remove duplicates from 38  
40 Bronchodilator Agents/ [start of tx]  
41 Cholinergic Antagonists/  
42 Adrenergic beta-Agonists/  
43 Adrenergic beta-2 Receptor Agonists/  
44 "Nebulizers and Vaporizers"/  
45 Expectorants/  
46 Muscarinic Antagonists/  
47 Adrenal Cortex Hormones/  
48 Albuterol/  
49 Fenoterol/  
50 Ipratropium/  
51 Terbutaline/  
52 Bronchodilat\$.ti,ab.  
53 (anticholinergic\$ or anti-cholinergic\$).ti,ab.  
54 (beta\$ adj3 (agonist\$ or adrenergic or adrenoceptor)).ti,ab.  
55 (SABA\$ or LABA\$).ti,ab.  
56 Albuterol.ti,ab.  
57 Salbutamol.ti,ab.  
58 Fenoterol.ti,ab.  
59 Levalbuterol.ti,ab.  
60 Xopenex HFA.ti,ab.  
61 Pirbuterol.ti,ab.  
62 Maxair Autohaler.ti,ab.  
63 Terbutaline.ti,ab.  
64 Spiriva.ti,ab.  
65 Arformoterol.ti,ab.  
66 Brovana.ti,ab.  
67 Formoterol.ti,ab.

## Appendix A. Detailed Methods

- 68 Foradil.ti,ab.
- 69 Indacaterol.ti,ab.
- 70 breexhaler.ti,ab.
- 71 Arcapta.ti,ab.
- 72 Salmeterol.ti,ab.
- 73 Serevent diskus.ti,ab.
- 74 Olodaterol.ti,ab.
- 75 Vilanterol.ti,ab.
- 76 Umeclidinium.ti,ab.
- 77 muscarin\$ antagonist\$.ti,ab.
- 78 antimuscarin\$.ti,ab.
- 79 anti muscarin\$.ti,ab.
- 80 (SAMA\$ or LAMA\$).ti,ab.
- 81 Ipratropium.ti,ab.
- 82 Aclidinium.ti,ab.
- 83 Tudorza Pressair.ti,ab.
- 84 (Glycopyrronium or glycopyrrolate).ti,ab.
- 85 Seebri.ti,ab.
- 86 Tiotropium.ti,ab.
- 87 Respimat.ti,ab.
- 88 HandiHaler.ti,ab.
- 89 Revefenacin.ti,ab.
- 90 glucocorticoid\$.ti,ab.
- 91 (inhal\$ and (corticosteroid\$ or steroid\$)).ti,ab.
- 92 Beclomethasone.ti,ab.
- 93 Qvar.ti,ab.
- 94 Betamethasone.ti,ab.
- 95 Budesonide.ti,ab.
- 96 Pulmicort flexhaler.ti,ab.
- 97 Ciclesonide.ti,ab.
- 98 Alvesco.ti,ab.
- 99 Symbicort.ti,ab.
- 100 Flunisolide.ti,ab.
- 101 Aerobid.ti,ab.
- 102 Fluticasone.ti,ab.
- 103 Flovent.ti,ab.
- 104 Mometasone.ti,ab.
- 105 Asmanex.ti,ab.
- 106 Triamcinolone.ti,ab.
- 107 Dry powder\$ inhaler\$.ti,ab.
- 108 Metered dose inhaler\$.ti,ab.
- 109 Breath actuated inhaler\$.ti,ab.
- 110 Accuhaler.ti,ab.
- 111 Turbohaler.ti,ab.
- 112 Diskhaler.ti,ab.
- 113 Nebuli?er\$.ti,ab.
- 114 Receptors, Interleukin-8B/  
115 ((CXCR2 or interleukin 8B or IL8B or IL-8B) adj3 (antagonis\$ or receptor\$)).ti,ab.

## Appendix A. Detailed Methods

- 116 CXC chemokine receptor 2.ti,ab.
- 117 (AZD5069 or AZD-5069).ti,ab.
- 118 (MK-7123 or MK7123 or Navarixin or SCH-527123).ti,ab.
- 119 (Danirixin or GSK1325756 or GSK-1325756).ti,ab.
- 120 (Elubrixin or SB-656933 or SB656933).ti,ab.
- 121 (SX-682 or SX682).ti,ab.
- 122 nonpharmacologic intervention\$.ti,ab.
- 123 non pharmacologic intervention\$.ti,ab.
- 124 Case Management/
- 125 "Delivery of Health Care, Integrated"/
- 126 Patient Care Management/
- 127 (Case management or Integrated care or Care coordination or coordinated care).ti,ab.
- 128 Counseling/
- 129 Directive Counseling/
- 130 Health Promotion/
- 131 Self-Management/
- 132 Risk Reduction Behavior/
- 133 health behavior/
- 134 Health Education/
- 135 Health Promotion/
- 136 Patient Education as Topic/
- 137 Healthy lifestyle/
- 138 counsel\$.ti,ab.
- 139 (advice or advise or consultation\$.ti,ab.
- 140 (behavio\$ adj2 (therap\$ or chang\$ or modification\$ or improv\$)).ti,ab.
- 141 (monitoring adj1 (patient\$ or activity or health)).ti,ab.
- 142 (set\$ adj2 goal\$).ti,ab.
- 143 action plan\$.ti,ab.
- 144 (assessment adj5 feedback).ti,ab.
- 145 support planning.ti,ab.
- 146 risk factor management.ti,ab.
- 147 (life style or lifestyle).ti,ab.
- 148 motivation\$.ti,ab.
- 149 health coach\$.ti,ab.
- 150 health behavio\$.ti,ab.
- 151 health education.ti,ab.
- 152 education\$ program\$.ti,ab.
- 153 patient education.ti,ab.
- 154 self manag\$.ti,ab.
- 155 (self adj (model or plan)).ti,ab.
- 156 (promot\$ adj3 (health or exercise\$ or physical activit\$ or weight loss)).ti,ab.
- 157 Smoking cessation/
- 158 "Tobacco Use Cessation"/
- 159 Smoking Prevention/
- 160 ((smok\$ or cigarette\$) adj10 (cessation or quit\$ or stop\$ or abstain\$ or abstinence)).ti,ab.
- 161 Diet, Reducing/ or nutrition therapy/ or nutritional support/
- 162 Feeding behavior/
- 163 Healthy diet/

## Appendix A. Detailed Methods

164 Weight Reduction Programs/  
165 (diet or diets or dietary or nutrition).ti.  
166 Exercise/  
167 Exercise Therapy/ or Exercise Movement Techniques/  
168 (exercis\$ or physical activit\$).ti.  
169 or/40-168  
170 8 and 169  
171 Pulmonary Disease, Chronic Obstructive/dt  
172 Bronchitis, Chronic/dt  
173 Lung Diseases, Obstructive/dt  
174 or/170-173  
175 36 and 174  
176 limit 175 to (english language and yr="2015 -Current")  
177 Mortality/ [start of tx harms]  
178 Morbidity/  
179 Death/  
180 "Drug-Related Side Effects and Adverse Reactions"/  
181 safety.ti,ab.  
182 harm\$.ti,ab.  
183 mortality.ti,ab.  
184 toxicity.ti,ab.  
185 complication\$.ti,ab.  
186 (death or deaths).ti,ab.  
187 (adverse adj2 (interaction\$ or response\$ or effect\$ or event\$ or reaction\$ or outcome\$)).ti,ab.  
188 side effect\$.ti,ab.  
189 adverse effects.fs.  
190 toxicity.fs.  
191 mortality.fs.  
192 Dizziness/  
193 Headache/  
194 Xerostomia/  
195 Constipation/  
196 Urinary Retention/  
197 Urinary Tract Infections/  
198 Muscle Cramp/  
199 Hematoma/  
200 Candidiasis, Oral/  
201 Bone Density/de [Drug Effects]  
202 Fractures, Bone/  
203 Cataract/  
204 Glaucoma/  
205 Glaucoma, open-angle/  
206 Cough/  
207 Bronchial Spasm/  
208 Arrhythmias, Cardiac/  
209 Tachycardia/  
210 Heart Failure/  
211 Heart Arrest/

## Appendix A. Detailed Methods

- 212 Heart Rate/de [Drug Effects]
- 213 Myocardial Infarction/
- 214 Cardiomyopathies/
- 215 xerostomia\$.ti,ab.
- 216 dry mouth.ti,ab.
- 217 headache\$.ti,ab.
- 218 tremor\$.ti,ab.
- 219 constipat\$.ti,ab.
- 220 urinary retention.ti,ab.
- 221 urinary tract infection\$.ti,ab.
- 222 muscle cramp\$.ti,ab.
- 223 (bruise\$ or bruising).ti,ab.
- 224 h?ematoma\$.ti,ab.
- 225 (((oral or oropharyngeal) adj candidiasis) or moniliasis).ti,ab.
- 226 ((low or decrease\$) adj3 (bone mass density or BMD)).ti,ab.
- 227 fracture\$.ti,ab.
- 228 cataract\$.ti,ab.
- 229 glaucoma.ti,ab.
- 230 paradoxical bronchospasm\$.ti,ab.
- 231 bronchial spasm\$.ti,ab.
- 232 respiratory death\$.ti,ab.
- 233 cardiovascular event\$.ti,ab.
- 234 arrhythm\$.ti,ab.
- 235 tachycardi\$.ti,ab.
- 236 palpitation\$.ti,ab.
- 237 ((rapid or increase\$ or elevat\$) adj3 (heart rate or heartbeat)).ti,ab.
- 238 myocardial infarction\$.ti,ab.
- 239 cardiomyopath\$.ti,ab.
- 240 (heart adj (failure\$ or attack\$)).ti,ab.
- 241 cardiac death\$.ti,ab.
- 242 (respiratory infection\$ or respiratory tract infection\$ or throat irritation or pharyngitis or sinusitis or rhinitis).ti,ab.
- 243 (myalgia or pain or back problem\$ or headache).ti,ab.
- 244 (dyspepsia or constipation or vomiting or gastroenteritis or gastrointestinal discomfort or stomach ache or diarrhea or nausea).ti,ab.
- 245 (voice alteration or dysphonia or otitis media or conjunctivitis or nasal congestion or nasal discharge or epistaxis).ti,ab.
- 246 (fever or pyrexia or edema or rash or dysmenorrhea or dizziness).ti,ab.
- 247 (infection or flu syndrome or pneumonia).ti,ab.
- 248 or/177-247
- 249 174 and 248
- 250 limit 249 to (english language and yr="2015 -Current")
- 251 39 or 176 or 250
- 252 251 not (animals/ not humans/)
- 253 252 not ((exp infant/ or child/ or adolescence/) not (exp adult/ or exp aged/ or middle aged/))
- 254 remove duplicates from 253

## Appendix A. Detailed Methods

### *Cochrane Central Register of Controlled Clinical Trials (CENTRAL)*

ID	Search	Hits	
#1	"chronic obstructive pulmonary" next disease*:	ti,ab,kw	
#2	"chronic obstructive airway" next disease*:	ti,ab,kw	
#3	"chronic airflow" next limitation*:	ti,ab,kw	
#4	"chronic obstructive respiratory" next disease*:	ti,ab,kw	
#5	"obstructive lung" next disease*:	ti,ab,kw	
#6	"chronic bronchitis":	ti,ab,kw	
#7	COPD:	ti,ab,kw or COAD:	ti,ab,kw
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7	21043	
#9	(prescreen* or pre-screen* or screen*):	ti,ab,kw	
#10	(early or earlier):	ti,ab,kw near/3 (identif* or test* or detect*):	ti,ab,kw
#11	(spiromet* or bronchspiromet*):	ti,ab,kw	
#12	(respiratory or lung):	ti,ab,kw near/3 test*:	ti,ab,kw
#13	("peak flow" or "peak expiratory flow"):	ti,ab,kw	
#14	(famil* near/3 histor*):	ti,ab,kw	
#15	#9 or #10 or #11 or #12 or #13 or #14		
#16	#8 and #15 with Publication Year from 2015 to 2020, in Trials		
#17	(treat* or therap*):	ti	
#18	bronchodilat*:	ti,ab,kw	
#19	(anticholinergic* or anti-cholinergic*):	ti,ab,kw	
#20	beta*:	ti,ab,kw near/3 (agonist* or adrenergic or adrenoceptor):	ti,ab,kw
#21	(SABA or LABA):	ti,ab,kw	
#22	Albuterol:	ti,ab,kw	
#23	Salbutamol:	ti,ab,kw	
#24	Fenoterol:	ti,ab,kw	
#25	Levalbuterol:	ti,ab,kw	
#26	Xopenex HFA:	ti,ab,kw	
#27	Pirbuterol:	ti,ab,kw	



## Appendix A. Detailed Methods

- #28 Maxair Autohaler:ti,ab,kw
- #29 Terbutaline:ti,ab,kw
- #30 Spiriva:ti,ab,kw
- #31 Arformoterol:ti,ab,kw
- #32 Brovana:ti,ab,kw
- #33 Formoterol:ti,ab,kw
- #34 Foradil:ti,ab,kw
- #35 Indacaterol:ti,ab,kw
- #36 breezhaler:ti,ab,kw
- #37 Arcapta:ti,ab,kw
- #38 Salmeterol:ti,ab,kw
- #39 Serevent diskus:ti,ab,kw
- #40 Olodaterol:ti,ab,kw
- #41 Vilanterol:ti,ab,kw
- #42 (muscarin\* next antagonist\*):ti,ab,kw
- #43 antimuscarin\*:ti,ab,kw
- #44 (anti next muscarin\*):ti,ab,kw
- #45 (SAMA or LAMA):ti,ab,kw
- #46 Ipratropium:ti,ab,kw
- #47 Aclidinium:ti,ab,kw
- #48 Tudorza Pressair:ti,ab,kw
- #49 Glycopyrronium bromide:ti,ab,kw
- #50 Seebri,ab,kw
- #51 Tiotropium:ti,ab,kw
- #52 Respimat:ti,ab,kw
- #53 HandiHaler:ti,ab,kw
- #54 glucocorticoid\*:ti,ab,kw
- #55 corticosteroid\*:ti,ab,kw
- #56 inhaled next steroid\*:ti,ab,kw

## Appendix A. Detailed Methods

- #57 Beclomethasone:ti,ab,kw
- #58 Qvar:ti,ab,kw
- #59 Betamethasone:ti,ab,kw
- #60 Budesonide:ti,ab,kw
- #61 Pulmicort flexhaler:ti,ab,kw
- #62 Ciclesonide:ti,ab,kw
- #63 Alvesco:ti,ab,kw
- #64 Symbicort:ti,ab,kw
- #65 Flunisolide:ti,ab,kw
- #66 Aerobid:ti,ab,kw
- #67 Fluticasone:ti,ab,kw
- #68 Flovent:ti,ab,kw
- #69 Mometasone:ti,ab,kw
- #70 Asmanex:ti,ab,kw
- #71 Triamcinolone:ti,ab,kw
- #72 (dry next powder\* next inhaler\*):ti,ab,kw
- #73 (metered next dose\* next inhaler\*):ti,ab,kw
- #74 (breath next actuated\* next inhaler\*):ti,ab,kw
- #75 Accuhaler:ti,ab,kw
- #76 Turbohaler:ti,ab,kw
- #77 Diskhaler:ti,ab,kw
- #78 (nebulizer\* or nebuliser\*):ti,ab,kw
- #79 ((CXCR2 or interleukin 8B or IL8B or IL-8B) NEAR/3 (antagonis\* or receptor\*)):ti,ab,kw
- #80 "CXC chemokine receptor 2":ti,ab,kw
- #81 (AZD5069 or AZD-5069):ti,ab,kw
- #82 (MK-7123 or MK7123 or Navarixin or SCH-527123):ti,ab,kw
- #83 (Danirixin or GSK1325756 or GSK-1325756):ti,ab,kw
- #84 (Elubrixin or SB-656933 or SB656933):ti,ab,kw
- #85 (SX-682 or SX682):ti,ab,kw

## Appendix A. Detailed Methods

- #86 (nonpharmacologic or "non pharmacologic"):ti,ab,kw
- #87 ("case management" or "integrated care" or "care coordination" or "coordinated care"):ti,ab,kw
- #88 (counsel\* or advice or advise or consultation\*):ti,ab,kw
- #89 (behavio\* NEAR/2 (therap\* or chang\* or modification\* or improv\*)):ti,ab,kw
- #90 (monitoring NEAR/1 (patient\* or activity or health)):ti,ab,kw
- #91 (set\* NEAR/2 goal\*):ti,ab,kw
- #92 Action NEXT plan\*:ti,ab,kw
- #93 (assessment NEAR/5 feedback):ti,ab,kw
- #94 "support planning":ti,ab,kw
- #95 "risk factor management":ti,ab,kw
- #96 ("life style" or lifestyle):ti,ab,kw
- #97 motivation\*:ti,ab,kw
- #98 health NEXT coach\*:ti,ab,kw
- #99 health NEXT behavio\*:ti,ab,kw
- #100 "health education":ti,ab,kw
- #101 education\* NEXT program\*:ti,ab,kw
- #102 "patient education":ti,ab,kw
- #103 self NEXT manag\*:ti,ab,kw
- #104 (promot\* NEAR/3 (health or exercise\* or physical NEXT activit\* or weight NEXT loss)):ti,ab,kw
- #105 ((smok\* or cigarette\*) NEAR/10 (cessation or quit\* or stop\* or abstain\* or abstinence)):ti,ab,kw
- #106 (diet or diets or dietary or nutrition):ti
- #107 (exercis\* or physical NEXT activit\*):ti
- #108 {or #17-#107}
- #109 #8 and #108 with Publication Year from 2015 to 2020, in Trials
- #110 #16 or #109
- #111 #110 NOT conference:pt

## Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Populations	KQ 1: adults aged 40 and over, asymptomatic adults, adults who have physical symptoms that are undetected by the patient or the clinician (e.g., have mild dyspnea that goes unnoticed); or those who have nonspecific symptoms (e.g., sporadic sputum production or cough) that have gone unrecognized as being related to COPD.	KQ 1: Patients with diagnosed COPD or other respiratory conditions; patients with identified alpha-1 antitrypsin deficiency; pregnant women
	KQs 2, 3: adults* aged 40 and over with screen-detected fixed airway obstruction; screen-relevant adults, e.g., patients with mild (forced expiratory volume in one second [FEV1] ≥ 80% predicted) to moderate (FEV1 50-79%) COPD* or mean population FEV1 ≥ 60% predicted	KQs 2, 3: Patients with severe or very severe COPD; pregnant women; patients with identified alpha-1 antitrypsin deficiency
Setting	All KQs: Primary or specialty care or community-based settings; developed countries, as defined by Human Development Index (HDI) in “very high human development” category (>0.8)	All KQs: Inpatient settings
Interventions	KQ 1: Any screening method including pre-bronchodilator screening spirometry, questionnaires or risk assessment tools; peak flow meter; confirmatory post-bronchodilator spirometry	KQ 1: Testing used for disease monitoring or management, pulmonary imaging
	KQs 2, 3: Pharmacotherapy (including short and long acting beta-agonists, anticholinergics, inhaled corticosteroids, CXCR2 antagonists, or combinations of these treatments); Nonpharmacologic therapy (including case management, behavioral counseling, exercise therapy)	KQs 2, 3: Oxygen therapy; surgical therapies; lung transplant; treatment of acute exacerbations; systemic corticosteroids; phosphodiesterase-4 inhibitors; mucolytic agents; antibiotics†; ‡; acupuncture, herbal or over the counter supplements; whole body vibration therapy
Comparisons	All KQs: Usual care; placebo; no screening/treatment	All KQs: Active comparator
Outcomes	KQs 1, 2: All-cause mortality, disease specific mortality, COPD-related morbidity; HRQoL at ≥6 months followup	KQs 1, 2: Change in FEV1
	KQ 3: Serious adverse events requiring unexpected or unwanted medical attention and/or resulting in death (e.g., requiring hospitalization)	
Study Designs	KQs 1, 2: RCT	KQs 1, 2: Nonrandomized studies including cohort studies, case-control studies, case series
	KQ 3: RCTs included for KQ2, large registry studies of drug safety	
Study Quality	All KQs: Good- & fair-quality	All KQs: Poor-quality
Language	All KQs: English	All KQs: Non-English studies

\*Based on the GOLD criteria COPD classifications

## Appendix A Table 1. Inclusion and Exclusion Criteria

†Patients with severe disease would constitute a very small minority of those identified by asymptomatic screening spirometry and thus the treatment modalities recommended for these patients will not be considered in this evidence review (i.e. oxygen therapy, surgical treatment to reduce lung volume, and lung transplantation).

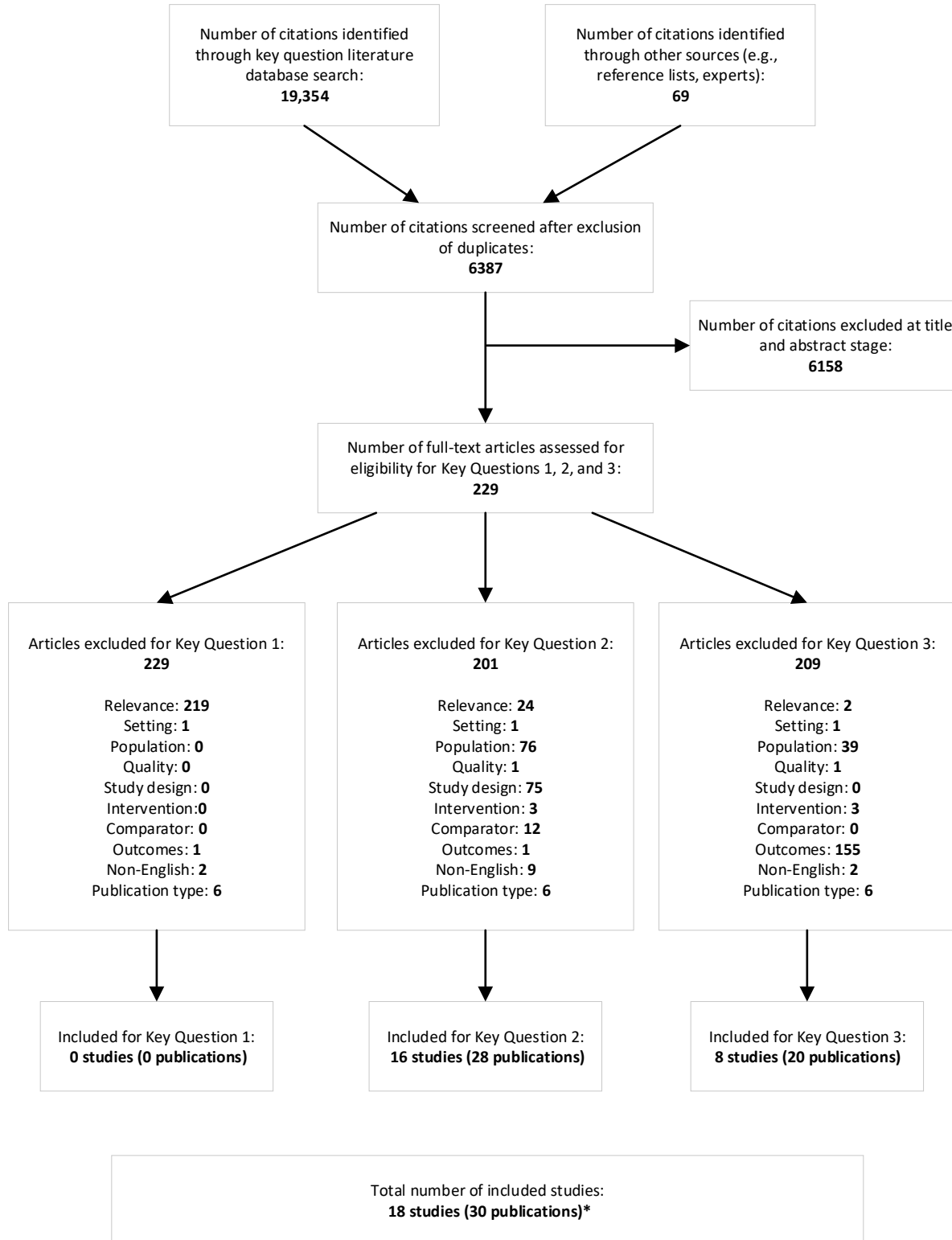
**Abbreviations:** COPD = chronic obstructive pulmonary disease; CXCR2 = CXC chemokine receptor 2; FEV<sub>1</sub> = forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQol = health related quality of life; RCT = randomized controlled trial

**Appendix A Table 2. Quality Assessment Criteria\***

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods <sup>3</sup>	<p><b>Bias arising in the randomization process or due to confounding</b></p> <ul style="list-style-type: none"> <li>• Valid random assignment/random sequence generation method used</li> <li>• Allocation concealed</li> <li>• Balance in baseline characteristics</li> </ul> <p><b>Bias in selecting participants into the study</b></p> <ul style="list-style-type: none"> <li>• Controlled Clinical Trial only: No evidence of biased selection of sample</li> </ul> <p><b>Bias due to departures from intended interventions</b></p> <ul style="list-style-type: none"> <li>• Fidelity to the intervention protocol</li> <li>• Low risk of contamination between groups</li> <li>• Participants were analyzed as originally allocated</li> </ul> <p><b>Bias from missing data</b></p> <ul style="list-style-type: none"> <li>• No, or minimal, post-randomization exclusions</li> <li>• Outcome data are reasonably complete and comparable between groups</li> <li>• Reasons for missing data are similar across groups</li> <li>• Missing data are unlikely to bias results</li> </ul> <p><b>Bias in measurement of outcomes</b></p> <ul style="list-style-type: none"> <li>• Blinding of outcome assessors</li> <li>• Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups</li> <li>• No evidence of inferential statistics</li> </ul> <p><b>Bias in reporting results selectively</b></p> <ul style="list-style-type: none"> <li>• No evidence that the measures, analyses, or subgroup analyses are selectively reported</li> </ul>
Registry studies, adapted from the Newcastle-Ottawa Scale <sup>60</sup>	<ul style="list-style-type: none"> <li>• Does the cohort appear to be valid?</li> <li>• Is the cohort representative of the average-risk patient?</li> <li>• Did the study adjust for prognostic variables?</li> <li>• Can we be confident in the assessment of the presence or absence of prognostic factors?</li> <li>• Can we be confident in the assessment of outcomes?</li> </ul>

\* Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent review.

## Appendix B Figure 1. Literature Flow Diagram



\*Articles may appear under more than one Key Question

## Appendix C. Included Studies List

*Included trials by author (ancillary publication(s) indented under primary article)*

Altenburg, WA, ten Hacken, NH, et al. Short- and long-term effects of a physical activity counselling programme in COPD: a randomized controlled trial. *Respir Med.* 109(1): 112-21. 2015.

Bischoff, EW, Akkermans, R, et al. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. *BMJ.* 345: e7642. 2012.

Fastenau, A, van Schayck, OC, et al. Effectiveness of an exercise training programme COPD in primary care: A randomized controlled trial. *Respir Med.* 165: 105943. 2020.

Jolly, K, Sidhu, MS, et al. Self management of patients with mild COPD in primary care: randomised controlled trial. *BMJ.* 361: k2241. 2018.

Jolly, K, Sidhu, M, et al. Improving recruitment to a study of telehealth management for COPD: a cluster randomised controlled 'study within a trial' (SWAT) of a multimedia information resource. *Trials [Electronic Resource].* 20(1): 453. 2019.

Sidhu, MS, Daley, A, et al. Patient self-management in primary care patients with mild COPD - protocol of a randomised controlled trial of telephone health coaching. *BMC Pulm Med.* 15: 16. 2015.

Liang, J, Abramson, MJ, et al. Interdisciplinary COPD intervention in primary care: a cluster randomised controlled trial. *Eur Respir J.* 53(4). 2019.

Markun, S, Rosemann, T, et al. Care in Chronic Obstructive Lung Disease (CAROL): a randomised trial in general practice. *Eur Respir J.* 51(5): 05. 2018.

Martinez, FJ, Rabe, KF, et al. Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Improves Lung Function versus Monotherapies in GOLD Category A Patients with COPD: Pooled Data from the Phase III PINNACLE Studies. *International Journal of Copd.* 15: 99-106. 2020.

Moy, ML, Martinez, CH, et al. Long-Term Effects of an Internet-Mediated Pedometer-Based Walking Program for Chronic Obstructive Pulmonary Disease: Randomized Controlled Trial. *J Med Internet Res.* 18(8): e215. 2016.

Moy, ML, Collins, RJ, et al. An Internet-Mediated Pedometer-Based Program Improves Health-Related Quality-of-Life Domains and Daily Step Counts in COPD: A Randomized Controlled Trial. *Chest.* 148(1): 128-137. 2015.

Nyberg, A, Tistad, M, et al. Can the COPD web be used to promote self-management in patients with COPD in swedish primary care: a controlled pragmatic pilot trial with 3 month- and 12 month follow-up. *Scand J Prim Health Care.* 37(1): 69-82. 2019.

Price, DB, Voorham, J, et al. Inhaled corticosteroids in COPD and onset of type 2 diabetes and osteoporosis: matched cohort study. *NPJ Primary Care Respiratory Medicine.* 29(1): 38. 2019.

Roman, M, Larraz, C, et al. Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomized controlled trial. *BMC Fam Pract.* 14: 21. 2013.

Tashkin, DP, Celli, B, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med.* 359(15): 1543-54. 2008.



## Appendix C. Included Studies List

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- Wang, MT, Liou, JT, et al. Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease: A Nested Case-Control Study. *JAMA Intern Med*. [Epub ahead of print]. 2018.
- Weldam, SWM, Schuurmans, MJ, et al. The effectiveness of a nurse-led illness perception intervention in COPD patients: a cluster randomised trial in primary care. *Erj Open Research*. 3(4): 2017.

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Zwar, NA, Bunker, JM, et al. Early intervention for chronic obstructive pulmonary disease by practice nurse and GP teams: a cluster randomized trial. *Fam Pract.* 33(6): 663-670. 2016.

## Appendix D. Excluded Studies List

Exclusion Code	Definition
E1	Study relevance
E2	Setting
E2a	Not Very High Human Development Index
E3	Population (general)
E3a	Not screen relevant population
E4	Study quality
E5	Study design
E6	Wrong intervention
E7	Wrong comparator
E8	No relevant outcomes
E9	Non-English publication
E10	Publication Type (i.e., conference abstract)

- Aljaafareh, A, Valle, JR, et al. Risk of cardiovascular events after initiation of long-acting bronchodilators in patients with chronic obstructive lung disease: A population-based study. *SAGE Open Medicine*. 4. 2050312116671337. 2016. **KQ1E1, KQ2E1, KQ3E3a**
- Anzueto, A, Jenkins, CR, et al. Efficacy of an inhaled corticosteroid/long-acting beta2-agonist combination in symptomatic COPD patients in GOLD groups B and D. *Eur Respir J*. 46(1): 255-8. 2015. **KQ1E1, KQ2E7, KQ3E8**
- Anzueto, AR, Kostikas, K, et al. Indacaterol/glycopyrronium versus salmeterol/fluticasone in the prevention of clinically important deterioration in COPD: results from the FLAME study. *Respir Res*. 19(1): 121. 2018. **KQ1E1, KQ2E7, KQ3E8**
- Arora, S, Delacruz, L, et al. 24-Hour Lung Function Following the Novel LAMA/LABA Co-Suspension Technology of Glycopyrrolate/Formoterol Fixed-Dose Combination MDI, in Patients with Moderate-to-Very-Severe COPD. *Am J Respir Crit Care Med*. 193(Meeting Abstracts): A6792. 2016. **KQ1E1, KQ2E5, KQ3E8**
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- through a program of patient selected goals. *Am J Respir Crit Care Med*. 191(Meeting Abstracts): A2458. 2015. **KQ1E1, KQ2E5, KQ3E8**
10. Bendstrup, KE, Ingemann Jensen, J, et al. Out-patient rehabilitation improves activities of daily living, quality of life and exercise tolerance in chronic obstructive pulmonary disease. *Eur Respir J*. 10(12): 2801-6. 1997. **KQ1E1, KQ2E3a, KQ3E8**
  11. Berry, MJ, Rejeski, WJ, et al. A lifestyle activity intervention in patients with chronic obstructive pulmonary disease. *Respir Med*. 104(6): 829-39. 2010. **KQ1E1, KQ2E3a, KQ3E8**
  12. Bestall, JC, Paul, EA, et al. Longitudinal trends in exercise capacity and health status after pulmonary rehabilitation in patients with COPD. *Respir Med*. 97(2): 173-80. 2003. **KQ1E1, KQ2E3a, KQ3E8**
  13. Blumenthal, JA, Emery, CF, et al. The effects of a telehealth coping skills intervention on outcomes in chronic obstructive pulmonary disease: primary results from the INSPIRE-II study. *Psychosom Med*. 76(8): 581-92. 2014. **KQ1E1, KQ2E5, KQ3E8**
  14. Boeselt, T, Nell, C, et al. Benefits of High-Intensity Exercise Training to Patients with Chronic Obstructive Pulmonary Disease: A Controlled Study. *Respiration*. 93(5): 301-310. 2017. **KQ1E1, KQ2E5, KQ3E8**
  15. Boland, Mr, Tsiachristas, A, et al. Copd Performance Indicators In An Integrated Care Program And Its Impact On Health Outcomes: the Recode Cluster Randomized Trial. *Value in health*. 18(7): A505. 2015. **KQ1E1, KQ2E5, KQ3E8**
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  17. Boxall, AM, Barclay, L, et al. Managing chronic obstructive pulmonary disease in the community. A randomized controlled trial of home-based pulmonary rehabilitation for elderly housebound patients. *J Cardiopulm Rehabil*. 25(6): 378-85. 2005. **KQ1E1, KQ2E3a, KQ3E8**
  18. Breyer, MK, Breyer-Kohansal, R, et al. Nordic walking improves daily physical activities in COPD: a randomised controlled trial. *Respir Res*. 11. 112. 2010. **KQ1E1, KQ2E3a, KQ3E8**
  19. Bringsvor, HB, Langeland, E, et al. Effects of a COPD self-management support intervention: a randomized controlled trial. *International Journal of Copd*. 13. 3677-3688. 2018. **KQ1E1, KQ2E3a, KQ3E8**
  20. Brooks, D, Krip, B, et al. The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease. *Eur Respir J*. 20(1): 20-9. 2002. **KQ1E1, KQ2E3a, KQ3E8**
  21. Bucknall, CE, Miller, G, et al. Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: randomised controlled trial. *BMJ*. 344. e1060. 2012. **KQ1E1, KQ2E3a, KQ3E8**
  22. Buhl, R, Magder, S, et al. Long-term general and cardiovascular safety of tiotropium/olodaterol in patients with moderate to very severe chronic obstructive pulmonary disease. *Respir Med*. 122. 58-66. 2017. **KQ1E1, KQ2E7, KQ3E8**

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23. Buhl, R, Maltais, F, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *Eur Respir J.* 45(4): 969-79. 2015. **KQ1E1, KQ2E7, KQ3E8**
24. Callejas Gonzalez, FJ, Genoves Crespo, M, et al. UPLIFT study - understanding potential long-term impacts on function with tiotropium - and sub-analyses. Bibliographic resume of the obtained results. *Expert Rev Respir Med.* 10(9): 1023-33. 2016. **KQ1E1, KQ2E5, KQ3E8**
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26. Casas, A, Troosters, T, et al. Integrated care prevents hospitalisations for exacerbations in COPD patients. *Eur Respir J.* 28(1): 123-30. 2006. **KQ1E1, KQ2E3a, KQ3E8**
27. Cascini, S, Kirchmayer, U, et al. Inhaled Corticosteroid Use in Chronic Obstructive Pulmonary Disease and Risk of Pneumonia: A Nested Case-Control Population-based Study in Lazio (Italy)-The OUTPUL Study. *Copd: Journal of Chronic Obstructive Pulmonary Disease.* 14(3): 311-317. 2017. **KQ1E1, KQ2E1, KQ3E3a**
28. Celli, Br, Decramer, M, et al. Defining a COPD composite safety endpoint for demonstrating efficacy in clinical trials: results from the randomized, placebo-controlled UPLIFT trial. *Respir Res.* 17(1). 2016. **KQ1E1, KQ2E3a, KQ3E8**
29. Chan, AW, Lee, A, et al. Effectiveness of a Tai chi Qigong program in promoting health-related quality of life and perceived social support in chronic obstructive pulmonary disease clients. *Qual Life Res.* 19(5): 653-64. 2010. **KQ1E1, KQ2E5, KQ3E8**
30. Chapron, A, Pele, F, et al. Targeted screening of COPD in primary care: feasibility and effectiveness. *Rev Mal Respir.* 2019. **KQ1E9, KQ2E9, KQ3E9**
31. Charususin, N, Gosselink, R, et al. Randomised controlled trial of adjunctive inspiratory muscle training for patients with COPD. *Thorax.* 73(10): 942-950. 2018. **KQ1E1, KQ2E5, KQ3E8**
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33. Chien, C-L, Liu, Y-F, et al. Impact of Multidisciplinary Self-Management Education Program in Patients with Chronic Obstructive Pulmonary Disease: self-Efficacy, Exercise Tolerance, and Quality of Life. *Am J Respir Crit Care Med.* 193(Meeting Abstracts): A7863. 2016. **KQ1E1, KQ2E5, KQ3E8**
34. Chiu, KL, Lee, CC, et al. Evaluating the association of osteoporosis with inhaled corticosteroid use in chronic obstructive pulmonary disease in Taiwan. *Sci Rep.* 11(1): 724. 2021. <https://dx.doi.org/10.1038/s41598-020-80815-y> **KQ1E1, KQ2E1, KQ3E3a**
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36. Coultas, D, Frederick, J, et al. A randomized trial of two types of nurse-assisted home care for patients with COPD. *Chest*. 128(4): 2017-24. 2005. **KQ1E1, KQ2E3a, KQ3E3a**
37. Coultas, D, Jackson, B, et al. A lifestyle physical activity intervention is associated with fewer self-reported COPD-related hospitalizations. *Eur Respir J*. 48(Suppl 60): Pa2060. 2016. **KQ1E10, KQ2E10, KQ3E10**
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39. Coultas, DB, Jackson, BE, et al. Home-based Physical Activity Coaching, Physical Activity, and Health Care Utilization in Chronic Obstructive Pulmonary Disease. Chronic Obstructive Pulmonary Disease Self-Management Activation Research Trial Secondary Outcomes. *Ann Am Thorac Soc*. 15(4): 470-478. 2018. **KQ1E1, KQ2E3a, KQ3E3a**
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41. Cruz, J, Brooks, D, et al. Walk2Bactive: A randomised controlled trial of a physical activity-focused behavioural intervention beyond pulmonary rehabilitation in chronic obstructive pulmonary disease. *Chron Respir Dis*. 13(1): 57-66. 2016. **KQ1E1, KQ2E5, KQ3E1**
42. de Roos, P, Lucas, C, et al. Effectiveness of a combined exercise training and home-based walking programme on physical activity compared with standard medical care in moderate COPD: a randomised controlled trial. *Physiotherapy*. 104(1): 116-121. 2018. **KQ1E1, KQ2E5, KQ3E8**
43. Dheda, K, Crawford, A, et al. Implementation of British Thoracic Society guidelines for acute exacerbation of chronic obstructive pulmonary disease: impact on quality of life. *Postgrad Med J*. 80(941): 169-71. 2004. **KQ1E1, KQ2E3a, KQ3E8**
44. Does Adherence to GOLD Recommendations Regarding Inhaler Therapy Lead to Better Patient Outcomes?: insights from the LOTT Trial. *Chest*. 158(2): 437-439. 2020. <https://dx.doi.org/10.1016/j.chest.2020.04.031> **KQ1E1, KQ2E5, KQ3E8**
45. Donohue, Jf, Bollu, V, et al. Improvements in health status for individuals with COPD treated with nebulized arformoterol tartrate: results from a 52-week trial. *Am J Respir Crit Care Med*. 191(Meeting Abstracts): A3983. 2015. **KQ1E1, KQ2E3a, KQ3E8**
46. Donohue, JF, Bollu, VK, et al. Long-term health-related quality-of-life and symptom response profiles with arformoterol in COPD: results from a 52-week trial. *International Journal of Copd*. 13. 499-508. 2018. **KQ1E1, KQ2E3a, KQ3E8**
47. Donohue, JF, Ganapathy, V, et al. Health Status of Patients with Moderate to Severe COPD after Treatment with Nebulized Arformoterol Tartrate or Placebo for 1 Year. *Clin Ther*. 39(1):

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- 66-74. 2017. **KQ1E1, KQ2E3a, KQ3E8**
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50. du Moulin, M, Taube, K, et al. Home-based exercise training as maintenance after outpatient pulmonary rehabilitation. *Respiration.* 77(2): 139-45. 2009. **KQ1E1, KQ2E6, KQ3E6**
51. Duruturk, N, Arikan, H, et al. A comparison of calisthenic and cycle exercise training in chronic obstructive pulmonary disease patients: a randomized controlled trial. *Expert Rev Respir Med.* 10(1): 99-108. 2016. **KQ1E1, KQ2E5, KQ3E8**
52. D'Urzo, A, Rennard, S, et al. A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease. *Respir Med.* 125: 39-48. 2017. **KQ1E1, KQ2E3a, KQ3E8**
53. Eaton, T, Young, P, et al. Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. *Respirology.* 14(2): 230-8. 2009. **KQ1E1, KQ2E5, KQ3E8**
54. Effects of low impact aerobic exercise in COPD. *Biomedical and pharmacology journal.* 13(1): 237-243. 2020. <https://dx.doi.org/10.13005/bpj/1881> **KQ1E1, KQ2E5, KQ3E8**
55. Efraimsson, EO, Hillervik, C, et al. Effects of COPD self-care management education at a nurse-led primary health care clinic. *Scand J Caring Sci.* 22(2): 178-85. 2008. **KQ1E1, KQ2E5, KQ3E8**
56. Elci, A, Borekci, S, et al. The efficacy and applicability of a pulmonary rehabilitation programme for patients with COPD in a secondary-care community hospital. *Respirology.* 13(5): 703-7. 2008. **KQ1E1, KQ2E5, KQ3E8**
57. Engstrom, CP, Persson, LO, et al. Long-term effects of a pulmonary rehabilitation programme in outpatients with chronic obstructive pulmonary disease: a randomized controlled study. *Scand J Rehabil Med.* 31(4): 207-13. 1999. **KQ1E1, KQ2E3a, KQ3E8**
58. Ernst, P, Coulombe, J, et al. The Risk of Sepsis with Inhaled and Oral Corticosteroids in Patients with COPD. *Copd: Journal of Chronic Obstructive Pulmonary Disease.* 14(2): 137-142. 2017. **KQ1E1, KQ2E1, KQ3E3a**
59. Farmer, A, Williams, V, et al. Self-Management Support Using a Digital Health System Compared With Usual Care for Chronic Obstructive Pulmonary Disease: Randomized Controlled Trial. *J Med Internet Res.* 19(5): e144. 2017. **KQ1E1, KQ2E3a, KQ3E3a**
60. Farmer, A, Williams, V, et al. Self-management support using an Internet-

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- linked tablet computer based intervention in chronic obstructive pulmonary disease (EDGE): randomised controlled trial. *Npj primary care respiratory medicine*. 26(16022): 10-cr024. 2016. **KQ1E10, KQ2E10, KQ3E10**
61. Ferguson, GT, Flezar, M, et al. Efficacy of Tiotropium + Olodaterol in Patients with Chronic Obstructive Pulmonary Disease by Initial Disease Severity and Treatment Intensity: A Post Hoc Analysis. *Adv Ther*. 32(6): 523-36. 2015. **KQ1E1, KQ2E7, KQ3E8**
62. Ferguson, GT, Kerwin, EM, et al. Health-Related Quality of Life Improvements in Moderate to Very Severe Chronic Obstructive Pulmonary Disease Patients on Nebulized Glycopyrrolate: Evidence from the GOLDEN Studies. *Chronic Obstructive Pulmonary Diseases*. 5(3): 193-207. 2018. **KQ1E1, KQ2E5, KQ3E8**
63. Ferguson, GT, Papi, A, et al. Budesonide/formoterol MDI with co-suspension delivery technology in COPD: the TELOS study. *Eur Respir J*. 52(3): 09. 2018. **KQ1E1, KQ2E7, KQ3E8**
64. Finnerty, JP, Keeping, I, et al. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. *Chest*. 119(6): 1705-10. 2001. **KQ1E1, KQ2E3a, KQ3E8**
65. Freund, T, Peters-Klimm, F, et al. Medical Assistant-Based Care Management for High-Risk Patients in Small Primary Care Practices: A Cluster Randomized Clinical Trial. *Ann Intern Med*. 164(5): 323-30. 2016. **KQ1E1, KQ2E3a, KQ3E3a**
66. Gallefoss, F, Bakke, PS, et al. Quality of life assessment after patient education in a randomized controlled study on asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 159(3): 812-7. 1999. **KQ1E1, KQ2E3a, KQ3E8**
67. Gallo-Silva, B, Cerezer-Silva, V, et al. Effects of Water-Based Aerobic Interval Training in Patients With COPD: A RANDOMIZED CONTROLLED TRIAL. *J Cardiopulm Rehabil Prev*. 39(2): 105-111. 2019. **KQ1E1, KQ2E5, KQ3E8**
68. Gayle, A, Dickinson, S, et al. Incidence of type II diabetes in chronic obstructive pulmonary disease: a nested case-control study. *NPJ Primary Care Respiratory Medicine*. 29(1): 28. 2019. **KQ1E1, KQ2E1, KQ3E3a**
69. Gon, Y, Nishi, K, et al. Efficacy and safety of glycopyrrolate/formoterol fumarate metered dose inhaler delivered using co-suspension delivery technology in Japanese patients with moderate-to-very severe chronic obstructive pulmonary disease. *Respir Investig*. 59(1): 135-144. 2021. <https://dx.doi.org/10.1016/j.resinv.2020.06.007> **KQ1E1, KQ2E3a, KQ3E8**
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71. Gonzalez, AV, Coulombe, J, et al. Long-term Use of Inhaled Corticosteroids in COPD and the Risk of Fracture. *Chest*. 153(2): 321-328. 2018. **KQ1E1, KQ2E1, KQ3E3a**
72. Gottlieb, V, Lyngso, AM, et al. Pulmonary rehabilitation for moderate COPD (GOLD 2)--does it have an effect?. *COPD*. 8(5): 380-6. 2011. **KQ1E1, KQ2E4, KQ3E4**



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73. Hakim, A, Khan, Y, et al. Low-Dose Budesonide/Formoterol Counteracts Airway Inflammation and Improves Lung Function in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 199(5): 662-664. 2019. **KQ1E1, KQ2E5, KQ3E8**
74. Hanania, NA, Papi, A, et al. Efficacy and safety of two doses of budesonide/formoterol fumarate metered dose inhaler in COPD. *Erj Open Research.* 6(2). 2020. **KQ1E1, KQ2E7, KQ3E8**
75. Hanania, NA, Sethi, S, et al. Long-term safety and efficacy of formoterol fumarate inhalation solution in patients with moderate-to-severe COPD. *International Journal of Copd.* 14. 117-127. 2019. **KQ1E1, KQ2E3a, KQ3E8**
76. He, GX, Li, N, et al. Benefits of different intensities of pulmonary rehabilitation for patients with moderate-to-severe COPD according to the GOLD stage: a prospective, multicenter, single-blinded, randomized, controlled trial. *International Journal of Copd.* 14. 2291-2304. 2019. **KQ1E2a, KQ2E2a, KQ3E2a**
77. Hermiz, O, Comino, E, et al. Randomised controlled trial of home based care of patients with chronic obstructive pulmonary disease. *BMJ.* 325(7370): 938. 2002. **KQ1E1, KQ2E5, KQ3E8**
78. Hernandez, C, Casas, A, et al. Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients. *Eur Respir J.* 21(1): 58-67. 2003. **KQ1E1, KQ2E5, KQ3E8**
79. Hernandez, M, Zambom-Ferraresi, F, et al. Short and long term effects of a physical activity programa in COPD patients. *Eur Respir J.* 2015. **KQ1E10, KQ2E10, KQ3E10**
80. Hernandez, MT, Rubio, TM, et al. Results of a home-based training program for patients with COPD. *Chest.* 118(1): 106-14. 2000. **KQ1E1, KQ2E5, KQ3E8**
81. Holland, AE, Mahal, A, et al. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. *Thorax.* 72(1): 57-65. 2017. **KQ1E1, KQ2E3a, KQ3E8**
82. Hoogendoorn, M, van Wetering, CR, et al. Self-report versus care provider registration of healthcare utilization: impact on cost and cost-utility. *Int J Technol Assess Health Care.* 25(4): 588-95. 2009. **KQ1E1, KQ2E5, KQ3E8**
83. Horne, BD, Hegewald, MJ, et al. The Summit Score Stratifies Mortality and Morbidity in Chronic Obstructive Pulmonary Disease. *International Journal of Copd.* 15. 1741-1750. 2020. <https://dx.doi.org/10.2147/COPD.S254437> **KQ1E1, KQ2E5, KQ3E8**
84. Hospes, G, Bossenbroek, L, et al. Enhancement of daily physical activity increases physical fitness of outclinic COPD patients: results of an exercise counseling program. *Patient Educ Couns.* 75(2): 274-8. 2009. **KQ1E1, KQ2E5, KQ3E8**
85. Howard, C, Dupont, S. 'The COPD breathlessness manual': a randomised controlled trial to test a cognitive-behavioural manual versus information booklets on health service use, mood and health status, in patients with chronic obstructive pulmonary disease. *NPJ Prim Care Respir Med.* 24. 14076. 2014. **KQ1E1, KQ2E3a, KQ3E8**
86. Huang, TM, Kuo, KC, et al. Risk of active tuberculosis among COPD patients treated with fixed combinations of long-acting beta2 agonists and

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- Randomized, Double-Blind, Placebo-Controlled Studies. *International Journal of Copd*. 15. 2309-2318. 2020. <https://dx.doi.org/10.2147/COPD.S267249> **KQ1E1, KQ2E5, KQ3E8**
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107. Lee, JH, Park, YH, et al. Risk of Pneumonia Associated with Inhaled Corticosteroid in Patients with Chronic Obstructive Pulmonary Disease: A Korean Population-Based Study. *International Journal of Copd*. 15. 3397-3406. 2020. <https://dx.doi.org/10.2147/COPD.S286149> **KQ1E1, KQ2E1, KQ3E3a**
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123. Magnussen, H, Arzt, M, et al. The Effect of Aclidinium Bromide 400 µg on Lung Function, Sleep Quality and Physical Activity in Patients with Chronic Obstructive Pulmonary Disease: results of a Phase IV Pilot Study. *Am J Respir Crit Care Med*.

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- 193(Meeting Abstracts): A6820. 2016. **KQ1E1, KQ2E5, KQ3E8**
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- severity and age; pooled analysis of GOLDEN 3 and GOLDEN 4. *International Journal of Copd*. 14. 27-37. 2019. **KQ1E1, KQ2E5, KQ3E8**
137. Orme, MW, Weedon, AE, et al. Findings of the Chronic Obstructive Pulmonary Disease-Sitting and Exacerbations Trial (COPD-SEAT) in Reducing Sedentary Time Using Wearable and Mobile Technologies With Educational Support: Randomized Controlled Feasibility Trial. *JMIR Mhealth Uhealth*. 6(4): e84. 2018. **KQ1E1, KQ2E5, KQ3E8**
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143. Rea, H, McAuley, S, et al. A chronic disease management programme can reduce days in hospital for patients with chronic obstructive pulmonary disease. *Intern Med J*. 34(11): 608-14. 2004. **KQ1E1, KQ2E3a, KQ3E8**
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145. Reisner, C, Gottschlich, G, et al. 24-Hour Lung Function Profile of Novel Co-Suspension Technology Glycopyrrolate/Formoterol Metered Dose Inhaler Versus Placebo and Spiriva Respimat, in Patients with Moderate-To-Very-Severe Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 193(Meeting Abstracts): A6823. 2016. **KQ1E1, KQ2E5, KQ3E8**
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- evaluation. *Clin Respir J*. 11(4): 459-469. 2017. **KQ1E1, KQ2E3a, KQ3E3a**
149. Robinson, SA, Shimada, SL, et al. A web-based physical activity intervention benefits persons with low self-efficacy in COPD: results from a randomized controlled trial. *J Behav Med*. 42(6): 1082-1090. 2019. **KQ1E1, KQ2E5, KQ3E8**
150. Robinson, SA, Wan, ES, et al. Age and Attitudes Towards an Internet-Mediated, Pedometer-Based Physical Activity Intervention for Chronic Obstructive Pulmonary Disease: Secondary Analysis. 24058297. 3(2): e19527. 2020. <https://dx.doi.org/10.2196/19527> **KQ1E1, KQ2E5, KQ3E8**
151. Rutkowski, S, Rutkowska, A, et al. Virtual reality rehabilitation in patients with chronic obstructive pulmonary disease: a randomized controlled trial. *International journal of COPD*. 15. 117-124. 2020. **KQ1E1, KQ2E5, KQ3E8**
152. Saeed, MI, Eklof, J, et al. Use of inhaled corticosteroids and the risk of developing type 2 diabetes in patients with chronic obstructive pulmonary disease. *Diabetes Obes Metab*. 22(8): 1348-1356. 2020. **KQ1E1, KQ2E1, KQ3E3a**
153. Samp, JC, Joo, MJ, et al. Risk of Cardiovascular and Cerebrovascular Events in COPD Patients Treated With Long-Acting beta2-Agonist Combined With a Long-Acting Muscarinic or Inhaled Corticosteroid. *Annals of Pharmacotherapy*. 51(11): 945-953. 2017. **KQ1E1, KQ2E1, KQ3E3a**
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155. Sethi, S, Donohue, JF, et al. Efficacy and safety of revefenacin for nebulization in patients with chronic obstructive pulmonary disease taking concomitant ICS/LABA or LABA: subgroup analysis from phase III trials. *Ther Adv Respir Dis*. 14. 1753466620905278. 2020. **KQ1E1, KQ2E5, KQ3E8**
156. Siler, TM, Donald, AC, et al. A randomized, parallel-group study to evaluate the efficacy of umeclidinium/vilanterol 62.5/25 mug on health-related quality of life in patients with COPD. *International Journal of Copd*. 11. 971-9. 2016. **KQ1E1, KQ2E5, KQ3E8**
157. Siler, Tm, Donald, Ac, et al. A randomized, parallel-group study to evaluate the efficacy of umeclidinium/vilanterol 62.5/25 mug on health-related quality of life in patients with COPD. *International journal of COPD*. 11(1): 971-979. 2016. **KQ1E1, KQ2E5, KQ3E8**
158. Siler, TM, Nagai, A, et al. A randomised, phase III trial of once-daily fluticasone furoate/vilanterol 100/25 mug versus once-daily vilanterol 25 mug to evaluate the contribution on lung function of fluticasone furoate in the combination in patients with COPD. *Respir Med*. 123. 8-17. 2017. **KQ1E1, KQ2E7, KQ3E8**
159. Silva, Cmdse, Gomes Neto, M, et al. Effects of upper limb resistance exercise on aerobic capacity, muscle strength, and quality of life in COPD patients: a randomized controlled trial. *Clin Rehabil*. 32(12): 1636-1644. 2018. **KQ1E1, KQ2E5, KQ3E8**

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160. Singh, D, Fuhr, R, et al. A Randomized Trial of Dual-Acting Bronchodilator AZD8871 for Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 199(10): 1282-1284. 2019. **KQ1E1, KQ2E5, KQ3E8**
161. Singh, D, Emirova, A, et al. Efficacy and safety of CHF6001, a novel inhaled PDE4 inhibitor in COPD: the PIONEER study. *Respir Res.* 21(1): 246. 2020. <https://dx.doi.org/10.1186/s12931-020-01512-y> **KQ1E1, KQ2E3a, KQ3E8**
162. Slok, AH, Kotz, D, et al. Effectiveness of the Assessment of Burden of COPD (ABC) tool on health-related quality of life in patients with COPD: a cluster randomised controlled trial in primary and hospital care. *BMJ Open.* 6(7): e011519. 2016. **KQ1E1, KQ2E3a, KQ3E3a**
163. Smith, JA, McGarvey, L, et al. The Effect of Aclidinium on Symptoms Including Cough in Chronic Obstructive Pulmonary Disease: A Phase 4, Double-Blind, Placebo-controlled, Parallel-Group Study. *Am J Respir Crit Care Med.* 200(5): 642-645. 2019. **KQ1E1, KQ2E5, KQ3E8**
164. Smith, JA. The Effect of Aclidinium on Symptoms Including Cough in COPD: a Phase IV, DoubleBlind, Placebo-Controlled, Parallel-Group Study. *Am J Respir Crit Care Med.* 2019. **KQ1E1, KQ2E5, KQ3E8**
165. Snoeck-Stroband, JB, Lapperre, TS, et al. Prediction of Long-Term Benefits of Inhaled Steroids by Phenotypic Markers in Moderate-to-Severe COPD: A Randomized Controlled Trial. *PLoS ONE [Electronic Resource].* 10(12): e0143793. 2015. **KQ1E1, KQ2E8, KQ3E8**
166. Stamenova, V, Liang, K, et al. Technology-Enabled Self-Management of Chronic Obstructive Pulmonary Disease With or Without Asynchronous Remote Monitoring: Randomized Controlled Trial. *J Med Internet Res.* 22(7): e18598. 2020. <https://dx.doi.org/10.2196/18598> **KQ1E1, KQ2E3a, KQ3E8**
167. Suissa, S, Dell'Aniello, S, et al. Concurrent use of long-acting bronchodilators in COPD and the risk of adverse cardiovascular events. *Eur Respir J.* 49(5): 05. 2017. **KQ1E1, KQ2E1, KQ3E3a**
168. Suissa, S, Dell'Aniello, S, et al. Inhaled corticosteroid use and the incidence of lung cancer in COPD. *Eur Respir J.* 55(2): 02. 2020. **KQ1E1, KQ2E1, KQ3E3a**
169. Suissa, S, Dell'Aniello, S, et al. Long-Acting Bronchodilator Initiation in COPD and the Risk of Adverse Cardiopulmonary Events: A Population-Based Comparative Safety Study. *Chest.* 151(1): 60-67. 2017. **KQ1E1, KQ2E1, KQ3E3a**
170. Sutanto, YS, Makhahah, DN, et al. Videogame assisted exercise training in patients with chronic obstructive pulmonary disease: A preliminary study. *Pulmonology.* 25(5): 275-282. 2019. **KQ1E1, KQ2E5, KQ3E8**
171. Tabak, M, Brusse-Keizer, M, et al. A telehealth program for self-management of COPD exacerbations and promotion of an active lifestyle: a pilot randomized controlled trial. *Int J Chron Obstruct Pulmon Dis.* 9: 935-44. 2014. **KQ1E1, KQ2E3a, KQ3E8**
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- 28(6): 582-91. 2014. **KQ1E1, KQ2E5, KQ3E8**
173. Tashkin, DP, Leimer, I, et al. Cardiac safety of tiotropium in patients with cardiac events: a retrospective analysis of the UPLIFT R trial. *Respir Res.* 16: 65. 2015. **KQ1E1, KQ2E3a, KQ3E8**
174. Tashkin, DP, Miravittles, M, et al. Concomitant inhaled corticosteroid use and the risk of pneumonia in COPD: a matched-subgroup post hoc analysis of the UPLIFT R trial. *Respir Res.* 19(1): 196. 2018. **KQ1E1, KQ2E3a, KQ3E8**
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176. Theander, K, Jakobsson, P, et al. Effects of pulmonary rehabilitation on fatigue, functional status and health perceptions in patients with chronic obstructive pulmonary disease: a randomized controlled trial. *Clin Rehabil.* 23(2): 125-36. 2009. **KQ1E1, KQ2E5, KQ3E8**
177. Thom, DH, Willard-Grace, R, et al. Randomized Controlled Trial of Health Coaching for Vulnerable Patients with Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc.* 15(10): 1159-1168. 2018. **KQ1E1, KQ2E3a, KQ3E3a**
178. van Wetering, CR, Hoogendoorn, M, et al. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax.* 65(1): 7-13. 2010. **KQ1E1, KQ2E3a, KQ3E8**
179. Varas, AB, Cordoba, S, et al. Effectiveness of a community-based exercise training programme to increase physical activity level in patients with chronic obstructive pulmonary disease: A randomized controlled trial. *Physiotherapy Research International.* 23(4): e1740. 2018. **KQ1E1, KQ2E3a, KQ3E8**
180. Vestbo, J, Fabbri, L, et al. Inhaled corticosteroid containing combinations and mortality in COPD. *Eur Respir J.* 52(6): 12. 2018. **KQ1E1, KQ2E5, KQ3E8**
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## Appendix D. Excluded Studies List

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## Appendix D. Excluded Studies List

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**Appendix E Table 1. Ongoing COPD Screening, Active Case-Finding, and Treatment Trials**

Study reference/ trial identifier	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	Status*
Primary Investigator						Estimated Completion
<b>Screening or active case-finding</b>						
NCT03583099 Fernando J Martinez MeiLan Han	The CAPTURE Study: Validating a Unique COPD Case Finding Tool in Primary Care (Aim 3) (CAPTURE)	United States	5000	Physician education and use of CAPTURE tool (screening questionnaire and PEF measurement)	COPD symptoms scores, exacerbations, hospitalization, mortality	Ongoing  Estimated completion: December 1, 2021
<b>Treatment</b>						
NCT03654092 Anja Frei	Home-based Exercise Training for COPD Patients (HOMEX-2)	Switzerland	120	Home-based exercise program	COPD symptoms, HRQoL, exacerbations	Recruiting  Estimated completion: October 2020
ACTRN12618001091291 Ian Yang	Mobile Health for Chronic Obstructive Pulmonary Disease (COPD)	Australia	100	COPD mobile health app (education, action plan, monitoring symptoms, modification of risk factors)	COPD symptoms, QoL, lifestyle changes, exacerbations, hospital admissions	Ongoing  Estimated completion: 2021
NCT03746873 Karin Wadell	Increase Level of Physical Activity and Decrease Use of Health Care for People With COPD (COPD)	Sweden	144	COPD Web: interactive web based tool to increase physical activity and appropriate self-management strategies	Pedometer with written information about physical activity	Recruiting  Estimated completion: March 15, 2022
NCT04139200 Thierry Troosters	Long-term Activity Coaching in Patients With COPD	Belgium	150	Long-term Activity Coaching in Patients With COPD	Health status, HRQoL, anxiety and depression	Ongoing  Estimated completion: November 2021

\*As of December 2021