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

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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$_1$] ≥ 80 percent predicted) to moderate (FEV$_1$ 50-79 percent predicted) COPD or a mean population FEV$_1$ ≥ 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, 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). This targeted update will be used by the USPSTF to update its 2016 recommendation using the reaffirmation process.

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 (FEV₁)/forced vital capacity (FVC) less than 0.70. COPD is a progressive, chronic condition without a known cure. COPD is characterized by continual respiratory decline associated with acute exacerbations that often result in hospitalization and ultimately death. 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.

COPD can be classified by the degree of obstruction, or symptoms, or both (Table 1). The degree of obstruction characterized by the post-bronchodilator FEV₁ 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). In addition to the severity of airflow limitation (i.e., spirometric grade), the 2020 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]). 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). Together the spirometric grade and letter grade corresponding to symptom burden can be used to guide management.

Prevalence and Risk Factors

In 2019, the Centers for Disease Control and Prevention (CDC) reported that chronic lower respiratory disease, composed chiefly of COPD, was the fourth leading cause of death in the United States, in spite of COPD-related mortality declining over the past 20 years. 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 2019 Behavioral Risk Factor Surveillance System (BRFSS) showed that 6.4 percent of adults reported having been diagnosed with COPD.\textsuperscript{12} A 2019 systematic review estimated that the prevalence of all stages of COPD in the Americas was 14.5 percent.\textsuperscript{13}

The major risk factor for developing COPD and COPD mortality is exposure to smoke or fumes, notably direct or indirect exposure to cigarette smoke.\textsuperscript{14} 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.\textsuperscript{15} 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.\textsuperscript{16, 17} 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.\textsuperscript{18} 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.\textsuperscript{14, 18-22} 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.\textsuperscript{23} 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.\textsuperscript{24}

COPD prevalence also appears to vary by sex and racial/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.\textsuperscript{11} 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.\textsuperscript{25} 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%).\textsuperscript{15} Analysis of data from BRFSS indicates that disproportionate socioeconomic challenges account for the comparatively high prevalence among Native American/Alaska Native populations.\textsuperscript{26} Native Americans also have the highest prevalence of current smoking that most other racial/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.\textsuperscript{27} 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), Latinx (17.0) and Asian (11.6) adults.\textsuperscript{28} 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.29

Screening and Active Case Finding

Many patients with COPD go undetected despite having symptoms for multiple reasons, including under-recognition 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.30-32 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.33, 34 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.35 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 FEV1 of around 71 percent predicted, compared with an FEV1 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.35 Other studies have demonstrated that screening or active case finding typically identifies persons with mild to moderate COPD or mean population FEV1 ≥ 60 percent.36-38

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],39, 40 the COPD Diagnostic Questionnaire [CDQ],41, 42 the COPD population screener [COPD-PS],43 and the Salzburg COPD-screening questionnaire [SCSQ]).44 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]).35, 46 Other ‘pre-screeners’ can include point of care tools measuring FEV known as ‘handheld spirometry’ (e.g., COPD-6 device [Vitalograph Ltd, Ireland]).47 Screening spirometry, either preceded by risk assessment or not, is administered without medication (i.e., pre-bronchodilator spirometry).4 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).4, 9 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.¹

**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.⁴,⁴⁸ The Lung Health Study demonstrated that smoking cessation counseling in adults with mostly asymptomatic mild to moderate COPD reduced all-cause mortality.⁴⁹,⁵⁰ 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).⁵¹ 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.²⁹,⁵² This underutilization may be due to a number of causes, including but not limited to low diagnostic yield and complexity of the testing.³⁷,⁵³-⁵⁹ 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.²¹ 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).⁶⁰ And
women were more than three times as likely than men to have severe disease at the time of diagnosis.61

**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).2 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.1 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., FEV1 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.1 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 α1-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 unrecognized as related to COPD.

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 FEV₁ ≥ 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. We supplemented these criteria with modified questions from the Newcastle-Ottawa Scale for nonrandomized studies of harms. 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 (SF-36) Health Survey (SF-36) or EuroQual (EQ-5D), as well as disease-specific measures like the St. George’s Respiratory Questionnaire.
Figure 1. Analytic Framework

(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. The CAT score can range from 0 to 40, with higher scores representing worse quality of life. 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 FEV₁ 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 FEV₁ 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 will be presented to the USPSTF and revisions in response to comments are reflected in this report. Additionally, a draft of this report will be posted for public comment on the USPSTF website along with the accompanying USPSTF draft recommendation statement.

USPSTF Involvement

This evidence update was funded by an AHRQ contract to support the USPSTF. We 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.
Figure 1. Analytic Framework

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)65-79 were included for KQ2, and eight studies (in 20 articles) for KQ3.81 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.65-79, 81 Three of these trials (n=20,058) evaluated inhaled bronchodilators (LAMA, LABA) and/or ICS,74, 75, 81 and 13 trials (n=3,658)65-73, 76-79 evaluated non-pharmacologic interventions (i.e., self-management interventions, exercise counseling interventions, supervised exercise and pulmonary rehabilitation interventions, and clinician education interventions).65-70, 72, 73, 76-79

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 FEV1 59.7% predicted) with a median followup of 1.8 years.75, 82 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 FEV1 59% predicted) (n=2603)83 and reduce exacerbations in patients with minimal symptoms (i.e., GOLD category A) (n=357) at 48 months.84

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. Only one of these two trials (n=114) demonstrated a reduction in COPD exacerbations at 65 weeks, the other trial (n=239) found no reduction in a composite outcome of exacerbations and pneumonia at 52 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. 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). 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). 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. 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 FEV1 of about 60 percent predicted, and a fairly high symptom score (i.e., SGRQ 45-56, CAT 18-19).

The UPLIFT trial (n=5993) 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) and GOLD category A patients (n=357). 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$_1$ was 59 percent predicted with a fairly high symptom score (i.e., SGRQ 41.5). In the GOLD category A subgroup analysis, the mean FEV$_1$ was 60.4 percent predicted but the mean symptom score was lower (i.e., SGRQ 16.8).

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). 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. 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) conducted in the UK, explicitly recruited minimally symptomatic persons with COPD (MRC score 1 or 2), and the mean FEV$_1$ 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$_1$'s were lower (60.6 and 65.4 percent).

Another four trials (n=83 to 1325) evaluated a web-only self-management intervention. 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. 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. In the other two trials the mean FEV<sub>1</sub> was 60.0 to 62.6 percent.\textsuperscript{76} \textsuperscript{77}

**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.\textsuperscript{65}

**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.\textsuperscript{57}

Two trials evaluated pulmonary rehabilitation programs; one trial (n=272) evaluated a home-based program,\textsuperscript{69} while the other trial (n=71) evaluated an intensive in person program.\textsuperscript{73} 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.\textsuperscript{69} 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.\textsuperscript{73}

**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.\textsuperscript{70} \textsuperscript{79} 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.\textsuperscript{79} As such, this trial tended to include persons with less
severe symptoms (mean SGQR 19.5, CAT 10.2) and airflow obstruction (mean FEV₁ 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 FEV₁ 67.3 percent predicted).70

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.71 Harms are discussed in Key Question 3.

The SUMMIT trial (n=16,590) in persons with mild to moderate COPD (mean FEV₁ 59.7 percent, SGQR 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.75, 82 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 UPLIFIT 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 FEV₁ of ≥100 mL, increase in SGQR total score from baseline ≥4 units [clinically meaningful difference], or moderate/severe exacerbation).83 Of note, these results are consistent with prior subgroup analyses by stage and FEV₁ included in the previous review and do not add any new understanding of the benefits of tiotropium over placebo in this population.86, 87 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]).84 The overall symptom score in these patients was low (i.e., SGQR 16.8), although the severity of airflow obstruction (FEV₁ 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 \(^{66,68}\) (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]).\(^{66}\) 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).\(^{68}\)

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’).\(^{77,85}\) The initial trial by Moy and colleagues (n analyzed=238) found no difference in exacerbations or pneumonia at 52 weeks;\(^{85}\) whereas the second trial by Wan and colleagues (n analyzed=109)\(^{77}\) 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]).\(^{77}\) 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).\(^{72,76,77,85}\) 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).\(^{72,76}\) 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).\(^{72,76,77,85}\) In addition, one trial found no benefit in smoking cessation at 26 weeks, using a variety of measures (Table 14).\(^{76}\)
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.65

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).73 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).67, 69, 73 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).67, 69, 73 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).69 Two trials reporting objective measures of physical performance found no improvement in the 6MWD at 26 and 52 weeks (Table 13).67, 73

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).79 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). 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. 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. The mean age in the observational studies was slightly older than the trial populations. The mean FEV1 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. 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. 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. 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 FEV1 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. 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. 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.

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).

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. 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). 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%). 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). 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.\textsuperscript{88-93} Comparative studies evaluating systematic screening approaches demonstrate that active case finding identifies more COPD than usual care.\textsuperscript{88, 94-96} 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.\textsuperscript{97}

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).\textsuperscript{36} 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).\textsuperscript{65-79, 85} 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.\textsuperscript{74, 75, 81} 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\textsubscript{1} 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.
Figure 1. Analytic Framework

Since the previous review, we have also newly included 13 trials evaluating non-pharmacologic interventions in mild to moderate, or minimally symptomatic, COPD.\textsuperscript{65-70, 72, 73, 76-79, 85} 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\textsubscript{1} 63 percent predicted).\textsuperscript{77} 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.\textsuperscript{80, 81} 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).\textsuperscript{98, 99} 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.\textsuperscript{100, 101}

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),\textsuperscript{102} as well as uptake of influenza and pneumococcal vaccination,\textsuperscript{103} remain suboptimal. Thus, interventions to increase smoking cessation success and vaccinations in persons with COPD remain an active area of research.\textsuperscript{104, 105} 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.\textsuperscript{106-108}

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).\textsuperscript{68, 76, 79} 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).\textsuperscript{109-114} 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.\textsuperscript{79} 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).

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
Figure 1. Analytic Framework

populations. Pulmonary rehabilitation, in general, has been demonstrated to improve exercise capacity, dyspnea, and quality of life in persons with COPD.\textsuperscript{115,116} 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.\textsuperscript{117-119} 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 \textit{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 \textit{a priori} defined health outcomes. We did not include physiologic changes in FEV\textsubscript{1} 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.\textsuperscript{120,121} 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\textsubscript{1} by about 5mL/year in trials reporting follow-up from 40 to 60 months.\textsuperscript{122}

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.\textsuperscript{8} Ongoing research is currently addressing these issues around diagnosis and treatment based on the pathological mechanisms (and their biomarkers) to develop and deliver treatment that can modify the natural course of disease, rather than symptom-based treatment.\textsuperscript{123}

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.

Third, the lack of \textit{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).46

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.
References


Figure 1. Analytic Framework

46. Yawn BP, Han M, Make BM, et al. Protocol Summary of the COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE)
Figure 1. Analytic Framework


10.1016/S0140-6736(16)30069-1
https://dx.doi.org/10.2147/COPD.S81295
https://dx.doi.org/10.1016/j.rmed.2020.105878
https://dx.doi.org/10.1186/s12931-020-01431-y
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Figure 1. Analytic Framework


105. Treheweys SP, Patel N, Turner AM. Interventions to Increase the Rate of Influenza and Pneumococcal Vaccination in Patients with Chronic Obstructive Pulmonary Disease: A Scoping Review. Medicina (Kaunas). 2019;55(6). 10.3390/medicina55060277


Figure 1. Analytic Framework

Figure 1. Analytic Framework

1. Screening for COPD
2. Screen detected COPD or mild to moderate COPD†
3. Treatment

- Reduced morbidity or mortality; improved HRQoL
- Harms

*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] ≥80% predicted) to moderate (FEV1 50% to 79%).

**Abbreviations:** COPD-chronic obstructive pulmonary disease; HRQoL=health-related quality of life.
<table>
<thead>
<tr>
<th>Classification of airflow limitation (post-BD FEV₁)</th>
<th>COPD Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild GOLD Stage I</td>
<td>FEV₁ ≥80% predicted</td>
<td></td>
</tr>
<tr>
<td>Moderate GOLD Stage II</td>
<td>FEV₁ ≥50% predicted but &lt;80% predicted</td>
<td></td>
</tr>
<tr>
<td>Severe GOLD Stage III</td>
<td>FEV₁ ≥30% predicted but &lt;50% predicted</td>
<td></td>
</tr>
<tr>
<td>Very severe GOLD Stage IV</td>
<td>FEV₁ &lt;30% predicted</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification of symptoms/risk of exacerbation</th>
<th>GOLD category A</th>
<th>mMRC 0-1 or CAT &lt;10 (low symptom burden)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>History of 0 or 1 moderate or severe exacerbations (not leading to hospital admission)</td>
<td></td>
</tr>
<tr>
<td>GOLD category B</td>
<td>mMRC ≥2 or CAT ≥10 (higher symptom burden)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of 0 or 1 moderate or severe exacerbations (not leading to hospital admission)</td>
<td></td>
</tr>
<tr>
<td>GOLD category C</td>
<td>mMRC 0-1 or CAT &lt;10 (low symptom burden)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)</td>
<td></td>
</tr>
<tr>
<td>GOLD category D</td>
<td>mMRC ≥2 or CAT ≥10 (higher symptom burden)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospital admission)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Counsel questionnaire; post-BD = post bronchodilator.
Table 2. Selected COPD Guidelines on Screening or Active Case-Finding

<table>
<thead>
<tr>
<th>Organization, year</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| GOLD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2020⁴         | GOLD states that the role of screening spirometry in the general population is controversial.  
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. |
| United Kingdom National Screening Committee (UK NSC), 2018¹²⁴                    | 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. The UK NSC does not mention active case finding. |
| American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and European Respiratory Society (ERS), 2011⁹       | The joint panel recommends against screening asymptomatic patients for COPD using spirometry, citing there was no evidence of benefit based on moderate-quality evidence. The panel recommends case finding with spirometry, in patients reporting COPD-related symptoms. |

*⁴Referenced 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

<table>
<thead>
<tr>
<th>Study, Year Quality</th>
<th>Country</th>
<th>N Randomized</th>
<th>Followup</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Treatment Comparison</th>
<th>Concomitant therapies allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINNACLE Martinez, 2020&lt;sup&gt;71&lt;/sup&gt; Fair</td>
<td>International</td>
<td>4983 (full population) GOLD category A subset: 729</td>
<td>24 weeks</td>
<td>40-80 years; smoking history of ≥10 pack-years; Post-BD FEV₁&lt;80% predicted; FEV₁/FVC≤70%</td>
<td>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 &gt; 12 hours/day</td>
<td>IG1: LAMA/LABA glycopyrrolate/formoterol fumarate (18/9.6 µg/twice a day) IG2: LAMA glycopyrrolate (18 µg/twice a day) IG3: LABA formoterol fumarate (9.6 µg/twice a day) CG: Placebo</td>
<td>Patients receiving stable dose of ICS at screening were permitted to continue</td>
</tr>
<tr>
<td>SUMMIT Vestbo, 2016&lt;sup&gt;75&lt;/sup&gt; Crim, 2017&lt;sup&gt;82&lt;/sup&gt; Good</td>
<td>International</td>
<td>16,590</td>
<td>4 years*</td>
<td>40-80 years; smoking history of ≥10 pack-years; Post-BD FEV₁ 50-70% predicted; FEV₁/FVC≤70%; score of ≥2 on mMRC dyspnea scale; history or increased risk of cardiovascular disease†</td>
<td>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</td>
<td>IG1: ICS/LABA fluticasone furoate/vilanterol (100/25 µg/day) IG2: LABA vilanterol (25 µg/day) IG3: ICS fluticasone furoate (100 µg/day) CG: Placebo</td>
<td>All ICS, LABA, and LAMA were discontinued, although other COPD medications such as theophyllines were allowed</td>
</tr>
</tbody>
</table>
Table 3. Key Question 2 Results: Study Characteristics for Included RCTs of Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Study, Year Quality</th>
<th>Country</th>
<th>N Randomized</th>
<th>Followup</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Treatment Comparison</th>
<th>Concomitant therapies allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPLIFT Decramer, 2009‡</td>
<td>International</td>
<td>5993 (full population)⁷⁴</td>
<td>4 years</td>
<td>≥ 40 years; smoking history of ≥10 pack-years; Post-BD FEV₁&lt;70% predicted; FEV₁/FVC≤70%§</td>
<td>History of asthma, COPD exacerbation or respiratory infection within 4 weeks before screening, a history of pulmonary resection, long-term oxygen therapy required &gt; 12 hours/day</td>
<td>IG: LAMA tiotropium bromide (18 µg/day) CG: Placebo</td>
<td>All respiratory medications except other SAMA or LAMA</td>
</tr>
<tr>
<td>Tashkin, 2012‡</td>
<td></td>
<td>2739⁸³, ⁸⁶ Stage I subset: 1210⁸⁷ GOLD category A subset: 357⁸⁴</td>
<td></td>
<td></td>
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<tr>
<td>Tashkin, 2008‡</td>
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<td></td>
</tr>
<tr>
<td>Halpin, 2015⁸⁴</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabe, 2020⁸³</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fair</td>
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</tr>
</tbody>
</table>

* 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 report¹²³
§ 23 patients had FEV₁>70 (protocol violation) but included in the analysis

**Abbreviations:** CG = control group; COPD = chronic obstructive pulmonary disease; FEV₁ = 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

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>N Randomized</th>
<th>Age, years (mean)</th>
<th>Female, %</th>
<th>Smoking status, %</th>
<th>Smoking history, pack-years (mean)</th>
<th>Number of exacerbations in the preceding year</th>
<th>Lung function post-BD FEV₁ % predicted of normal (mean)</th>
<th>HrQOL symptom score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINNACLE</td>
<td>GOLD A subset: 729</td>
<td>65.5</td>
<td>27.3%</td>
<td>Current: 32.8%; Former: 67.2%</td>
<td>45.6</td>
<td>NR</td>
<td>NR</td>
<td>CAT mean score: 6.5</td>
</tr>
<tr>
<td>Vestbo, 2016 Crim, 2017</td>
<td>Full population: 16,590</td>
<td>65</td>
<td>25.5%</td>
<td>Current: 46.6%; Former: 53.4%</td>
<td>41</td>
<td>1: 24.4% 2 or more: 14.8%</td>
<td>59.7</td>
<td>SGRQ total score mean: 45-46; CAT mean score: 18-19</td>
</tr>
<tr>
<td>Decramer, 2009 Tashkin, 2012 Tashkin, 2008 Halpin, 2015 Rabe, 2020</td>
<td>Stage II subset: 2,739</td>
<td>64.5</td>
<td>NR</td>
<td>Current: 33.0%; Former: 67.0%</td>
<td>47.5</td>
<td>NR</td>
<td>59</td>
<td>SGRQ total score mean: 41.5</td>
</tr>
<tr>
<td></td>
<td>FEV₁≥60% subset: 1,210</td>
<td>64</td>
<td>29.9%</td>
<td>Current: 32.3%; Former: 67.7%</td>
<td>47.6</td>
<td>NR</td>
<td>64</td>
<td>SGRQ total score mean: 40</td>
</tr>
<tr>
<td>GOLD category A: 357</td>
<td>65</td>
<td>18.5%</td>
<td>Current: 29.4%; Former: 70.6%</td>
<td>NR</td>
<td>NR</td>
<td>60.4</td>
<td>SGRQ total score mean: 16.8</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CAT = COPD Assessment Test; FEV₁ = 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

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Subgroup</th>
<th>Timing of analysis</th>
<th>Interaction testing performed?</th>
<th>Groups matched at baseline?</th>
<th>Controlled for confounders?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINNACLE Martinez, 2020&lt;sup&gt;71&lt;/sup&gt;</td>
<td>GOLD category A</td>
<td>Post-hoc&lt;sup&gt;*&lt;/sup&gt;</td>
<td>No†</td>
<td>Yes</td>
<td>No†</td>
</tr>
<tr>
<td>UPLIFT Decramer, 2009&lt;sup&gt;86&lt;/sup&gt;</td>
<td>COPD Stage II</td>
<td>A-priori</td>
<td>Yes (for exacerbations only)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>UPLIFT Tashkin, 2012&lt;sup&gt;87&lt;/sup&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;≥60% predicted</td>
<td>Post-hoc</td>
<td>No</td>
<td>Only difference is statistically significantly more smokers in CG than IG (36% versus 29% P=0.011)</td>
<td>For HrQOL analysis only</td>
</tr>
<tr>
<td>UPLIFT Halpin, 2015&lt;sup&gt;64&lt;/sup&gt;</td>
<td>GOLD category A</td>
<td>Post-hoc</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>UPLIFT Rabe, 2020&lt;sup&gt;83&lt;/sup&gt;</td>
<td>COPD Stage II</td>
<td>Post-hoc</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>*</sup> 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.<br><br><sup>†</sup> Performed for lung function outcomes but not for mortality or harms<br><br><sup>‡</sup> Included in previous report<sup>23</sup><br><br><sup>§</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>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study*</th>
<th>Country</th>
<th>Design</th>
<th>N Randomized</th>
<th>Followup</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-management</td>
<td>Bischoff, 2012&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>RCT</td>
<td>165</td>
<td>104 weeks</td>
<td>Aged 35 years and older and FEV&lt;sub&gt;1&lt;/sub&gt;/FVC&lt; 0.70</td>
<td>Post-BD FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 30% predicted, treatment by a respiratory physician, severe comorbid conditions with a reduced life expectancy, inability to communicate in the Dutch language</td>
</tr>
<tr>
<td></td>
<td>Jolly, 2018&lt;sup&gt;68&lt;/sup&gt; PSM COPD</td>
<td>United Kingdom</td>
<td>RCT</td>
<td>577</td>
<td>52 weeks</td>
<td>≥18 years, on the practice COPD register, mild dyspnea (MRC grades 1 or 2), FEV&lt;sub&gt;1&lt;/sub&gt;/FVC &lt;0.7</td>
<td>Considered to be inappropriate for the study by patients’ physician (e.g., terminal disease or a severe psychiatric disorder)</td>
</tr>
<tr>
<td></td>
<td>Moy, 2016&lt;sup&gt;95&lt;/sup&gt; Taking Healthy Steps</td>
<td>United States</td>
<td>RCT</td>
<td>239</td>
<td>52 weeks</td>
<td>≥ 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 &lt; 150 minutes of self-reported physical activity per week); physician clearance; regular email user with internet access</td>
<td>Quadriplegia/paraplegia or wheelchair dependence, dementia, pregnancy-related diagnoses/procedures in past year, involvement in another pedometer walking program</td>
</tr>
<tr>
<td></td>
<td>Nyberg, 2019&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Sweden</td>
<td>CCT</td>
<td>83</td>
<td>52 weeks</td>
<td>Diagnosis of COPD</td>
<td>Inability to communicate in Swedish</td>
</tr>
<tr>
<td></td>
<td>Voncken-Brewster, 2015&lt;sup&gt;76&lt;/sup&gt; MasterYourBreath</td>
<td>Netherlands</td>
<td>RCT</td>
<td>1325</td>
<td>26 weeks</td>
<td>Diagnosed with COPD or at moderate/high risk for COPD, aged 40–70, internet access and basic computer skills</td>
<td>Inability to communicate in the Dutch language</td>
</tr>
<tr>
<td></td>
<td>Wan, 2020&lt;sup&gt;77&lt;/sup&gt; ESC</td>
<td>United States</td>
<td>RCT</td>
<td>114</td>
<td>65 weeks</td>
<td>Aged ≥40 years, ≥10 pack-years of smoking, FEV&lt;sub&gt;1&lt;/sub&gt;/FVC &lt;0.70 or emphysema on a CT, able to walk one block, internet access and basic computer skills, &gt;90% accuracy on step counter</td>
<td>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, &lt;85% blood oxygen saturation during 6MWT</td>
</tr>
</tbody>
</table>
Table 6. Key Question 2 Results: Study Characteristics for Included Trials of Non-Pharmacologic Treatments

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study*</th>
<th>Country</th>
<th>Design</th>
<th>N Randomized</th>
<th>Followup</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weldam, 201778 COPD-GRIP</td>
<td>Netherlands</td>
<td>Cluster RCT</td>
<td>204</td>
<td>39 weeks</td>
<td>Diagnosed with COPD, age ≥40, a lung function test in previous year</td>
<td>Life-threatening comorbid condition or if they had a primary diagnosis of asthma, inability to communicate in the Dutch language</td>
<td></td>
</tr>
<tr>
<td>Exercise only</td>
<td>Altenburg, 201565 COACH</td>
<td>Netherlands</td>
<td>RCT</td>
<td>48†</td>
<td>Age 40-80, COPD diagnosed based on GOLD guidelines</td>
<td>Comorbidities which severely limit physical activity, exacerbations or respiratory tract infections within prior two months</td>
<td></td>
</tr>
<tr>
<td>Supervised exercise or pulmonary rehabilitation</td>
<td>Fastenau, 202067</td>
<td>Netherlands</td>
<td>RCT</td>
<td>90</td>
<td>Mild to moderate COPD, dyspnea, and physically inactive lifestyle</td>
<td>Pulmonary rehabilitation in the past year, lower respiratory tract infections in past 8 weeks, serious comorbid conditions</td>
<td></td>
</tr>
<tr>
<td>Liang, 201969 RADICALS</td>
<td>Australia</td>
<td>Cluster RCT</td>
<td>272</td>
<td>52 weeks</td>
<td>≥40 years, at least two clinic visits in past year, COPD diagnosed based on spirometry and clinical confirmation</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Roman, 201373</td>
<td>Spain</td>
<td>RCT</td>
<td>71</td>
<td>52 weeks</td>
<td>35 to 74 years old, moderate COPD based on GOLD guidelines</td>
<td>Musculoskeletal conditions that prevented exercising and walking test assessments, or terminal illness or other severe disease</td>
<td></td>
</tr>
<tr>
<td>Clinician education only</td>
<td>Markun, 201870 CAROL</td>
<td>Switzerland</td>
<td>Cluster RCT</td>
<td>216</td>
<td>≥45 years, ≥10 pack-years smoking history, FEV1/FVC&lt;0.7</td>
<td>Patients attending for emergency consultations, insufficient German language skills, asthma/hay fever, estimated life expectancy &lt;6 months</td>
<td></td>
</tr>
<tr>
<td>Zwar, 201679 PELICAN</td>
<td>Australia</td>
<td>Cluster RCT</td>
<td>254</td>
<td>52 weeks</td>
<td>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</td>
<td>Previously recorded diagnosis of COPD, Inability to communicate in English, cognitive impairment</td>
<td></td>
</tr>
</tbody>
</table>

* 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; FEV1 =...
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 Counsel 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

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study</th>
<th>Country</th>
<th>Intervention description</th>
<th>Delivery</th>
<th>Duration</th>
<th>Comparator</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-management</td>
<td>Bischoff, 2012&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>Tailored self-management education/support</td>
<td>2-4 in person sessions (1 hour) with nurse; 6 follow up phone calls</td>
<td>52 weeks</td>
<td>Usual care</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-tailored self-management education/support*</td>
<td>1-4 routine monitoring nursing visits</td>
<td>52 weeks</td>
<td>Usual care</td>
<td>NR</td>
</tr>
<tr>
<td>Jolly, 2018&lt;sup&gt;68&lt;/sup&gt; PSM COPD</td>
<td>United Kingdom</td>
<td>Telephone health coaching intervention to support self-management</td>
<td>4 nurse counseling telephone sessions (15-60 minutes) with tailored supportive materials</td>
<td>26 weeks</td>
<td>13-page informational leaflet on self-management</td>
<td>86.4% of scheduled calls were delivered and 75.4% of participants received all four calls</td>
<td></td>
</tr>
<tr>
<td>Moy, 2016&lt;sup&gt;85&lt;/sup&gt; Taking Healthy Steps</td>
<td>United States</td>
<td>Pedometer plus educational and tracking website with personalized goals</td>
<td>Web/computer based</td>
<td>17 weeks with 35 week maintenance phase</td>
<td>Received pedometer and access to step count website</td>
<td>Step counts recorded by 77% of intervention group and 64% of control group</td>
<td></td>
</tr>
<tr>
<td>Nyberg, 2019&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Sweden</td>
<td>COPD self-management website (COPD Web)</td>
<td>Use of pedometer and interactive webpage</td>
<td>52 weeks</td>
<td>Received pedometer and information on importance of physical activity</td>
<td>95% of participants created an account and visited the site at least once (77% of participants were considered users)</td>
<td></td>
</tr>
<tr>
<td>Voncken-Brewster, 2015&lt;sup&gt;%&lt;/sup&gt; MasterYour Breath</td>
<td>Netherlands</td>
<td>Web-based application providing computer-generated tailored feedback</td>
<td>Web/computer based</td>
<td>26 weeks</td>
<td>Usual care</td>
<td>36% of participants used application</td>
<td></td>
</tr>
<tr>
<td>Wan, 2020&lt;sup&gt;77&lt;/sup&gt; ESC</td>
<td>United States</td>
<td>Pedometer plus educational and tracking website with personalized goals</td>
<td>Web/computer based</td>
<td>13 weeks</td>
<td>Received pedometer and access to step count website</td>
<td>Overall percentage of wear days: 85.8% (average 15.2 hours per day), &gt;4 logins per month</td>
<td></td>
</tr>
<tr>
<td>Weldam, 2017&lt;sup&gt;78&lt;/sup&gt; COPD-GRIP</td>
<td>Netherlands</td>
<td>Nurse consultations discussing individual patient illness, behavior, and action plan formation</td>
<td>3 in-persons consultations (30 minutes); 4 hour educational session for nurses</td>
<td>6 weeks</td>
<td>Usual care</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Key Question 2 Results: Intervention Characteristics for Included Trials of Non-Pharmacologic Treatments

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

* Referred to in trial as ‘routine monitoring’.

**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; NR = Not reported.
Table 7. Key Question 2 Results: Intervention Characteristics for Included Trials of Non-Pharmacologic Treatments

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>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study</th>
<th>Age, years (mean)</th>
<th>Female, %</th>
<th>Smoking status, %</th>
<th>Smoking history, pack-years (mean)</th>
<th>Number of exacerbations in preceding year</th>
<th>Lung function post-BD FEV₁ % predicted of normal (mean)</th>
<th>COPD Stage</th>
<th>HrQOL symptom score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-management</td>
<td>Bischoff, 2012</td>
<td>64.9</td>
<td>35</td>
<td>Current: 30</td>
<td>NR</td>
<td>Median: 0.5 to 1</td>
<td>65.4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Jolly, 2018</td>
<td>70.4</td>
<td>37</td>
<td>Current: 23</td>
<td>NR</td>
<td>1 or more: 47%</td>
<td>71.7</td>
<td>1: 33%</td>
<td>2: 54% 3: 12% 4: &lt;1%</td>
</tr>
<tr>
<td></td>
<td>PSM COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SGRQ mean score:</td>
<td>28.7</td>
</tr>
<tr>
<td></td>
<td>Moy, 2016</td>
<td>66.8</td>
<td>6</td>
<td>Current: 24</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>mMRC 0-1:</td>
<td>69% mMRC 2-4: 31%</td>
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<td></td>
<td></td>
<td></td>
<td>1: 33%</td>
<td>2: 54% 3: 12% 4: &lt;1%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SGRQ mean score:</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Nyberg, 2019</td>
<td>68.0</td>
<td>43</td>
<td>Current: 19</td>
<td>30</td>
<td>NR</td>
<td>60.0</td>
<td>A: 53% B: 20%</td>
<td>C: 8% D: 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Former: 71</td>
<td></td>
<td></td>
<td></td>
<td>EQ-5D mean score:</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Voncken-Brewster, 2015</td>
<td>57.6</td>
<td>52</td>
<td>Current: 34</td>
<td>NR</td>
<td>NR</td>
<td>NR*</td>
<td>NR</td>
<td>CCQ mean score:</td>
</tr>
<tr>
<td></td>
<td>MasterYour Breath</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MRC score:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0: 27.5% 1: 40.1%</td>
</tr>
<tr>
<td></td>
<td>Wan, 2020</td>
<td>68.6</td>
<td>2</td>
<td>Current: 37</td>
<td>61.5</td>
<td>Mean in previous year: 0.35</td>
<td>62.6</td>
<td>NR</td>
<td>SGRQ mean score:</td>
</tr>
<tr>
<td></td>
<td>ESC</td>
<td></td>
<td></td>
<td>Former: 63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33.5</td>
</tr>
<tr>
<td></td>
<td>Weldam, 2017</td>
<td>67.0</td>
<td>55</td>
<td>Current: 30</td>
<td>NR</td>
<td>NR</td>
<td>60.6</td>
<td>1: 9%</td>
<td>2: 62% 3: 21% 4: 7%†</td>
</tr>
<tr>
<td></td>
<td>COPD-GRIP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MRC mean score:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.1</td>
</tr>
</tbody>
</table>
Table 8. Key Question 2 Results: Population Characteristics for Included Trials of Non-Pharmacologic Treatments

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study</th>
<th>Age, years (mean)</th>
<th>Female, %</th>
<th>Smoking status, %</th>
<th>Number of exacerbations in preceding year</th>
<th>Lung function post-BD FEV\textsubscript{1} % predicted of normal (mean)</th>
<th>COPD Stage</th>
<th>HrQOL symptom score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise only</td>
<td>Altenburg, 2015% COACH</td>
<td>65‡</td>
<td>33</td>
<td>NR</td>
<td>NR</td>
<td>78‡</td>
<td>1: 46%</td>
<td>2: 48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3: 8%</td>
<td>4: 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CRQ total mean: 117; CCQ total mean: 0.75</td>
<td></td>
</tr>
<tr>
<td>Supervised exercise or pulmonary rehabilitation</td>
<td>Fastenau, 2020%</td>
<td>62.5</td>
<td>51</td>
<td>Current: 38</td>
<td>NR</td>
<td>74.2</td>
<td>1: 27%</td>
<td>2: 73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Former: 54</td>
<td></td>
<td></td>
<td>CCQ total score mean: 1.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liang, 2019% RADICALS</td>
<td>64.5</td>
<td>39</td>
<td>Current: 61</td>
<td>NR</td>
<td>70.0</td>
<td>Mild: 70%</td>
<td>Moderate: 21% Severe: 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Former: 62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Roman, 2013%</td>
<td>64.2</td>
<td>18</td>
<td>Current: 34</td>
<td>39%§</td>
<td>60.3</td>
<td>2: 100%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Former: 62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Markun, 2018% CAROL</td>
<td>67.5</td>
<td>41</td>
<td>Current: 56</td>
<td>1 or more: 34%</td>
<td>67.3</td>
<td>A: 59%</td>
<td>B: 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Former: 44</td>
<td></td>
<td></td>
<td>C: 19%</td>
<td>D: 12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAT mean score: 10.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zwar, 2016% PELICAN</td>
<td>66.0</td>
<td>40</td>
<td>Current: 31</td>
<td>NR</td>
<td>74.6</td>
<td>1: 21%</td>
<td>2: 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Former: 69</td>
<td></td>
<td></td>
<td>3: 6%</td>
<td>4: &lt;1%ll</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SGQR mean score: 19.5; CAT: 10.2</td>
<td></td>
</tr>
</tbody>
</table>

*Diagnosed with COPD: 21.7%, increased risk for COPD 78.3% ‡ 78 patients (31%) that a clinician assigned a diagnosis of COPD were found to not meet criteria for COPD (FEV\textsubscript{1}/FVC not <0.7) upon further assessment § 39% with physician visit for exacerbation and 18% with hospitalization † 78 patients (31%) that a clinician assigned a diagnosis of COPD were found to not meet criteria for COPD (FEV\textsubscript{1}/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\textsubscript{1} = 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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Study, year</th>
<th>Treatment Comparison</th>
<th>Followup</th>
<th>Outcome</th>
<th>N analyzed</th>
<th>IG Events*</th>
<th>CG Events*</th>
<th>IG vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>SUMMIT Vestbo, 2016\textsuperscript{16} Crim, 2017\textsuperscript{52}</td>
<td>Fluticasone furoate vs. placebo</td>
<td>1.8 years (Median)</td>
<td>All-cause mortality</td>
<td>8246</td>
<td>251/4135 (6.1%)</td>
<td>275/4111 (6.7%)</td>
<td>HR: 0.91 (95% CI, 0.77 to 1.08)</td>
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<td></td>
<td></td>
<td>Annual rate of moderate/severe exacerbations</td>
<td>8246</td>
<td>0.31</td>
<td>0.35</td>
<td>Percent reduction: 12% (95% CI, 4% to 19%)</td>
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<td></td>
<td>Annual rate of hospitalized exacerbation</td>
<td>8246</td>
<td>0.06</td>
<td>0.07</td>
<td>Percent reduction: 18% (95% CI, 3% to 31%)</td>
</tr>
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<td>Composite CVD endpoint\textsuperscript{†}</td>
<td>8246</td>
<td>161/4135 (3.9%)</td>
<td>173/4111 (4.2%)</td>
<td>HR: 0.90 (95% CI, 0.73 to 1.11)</td>
</tr>
<tr>
<td>LABA</td>
<td>PINNACLE Martinez, 2020\textsuperscript{71}</td>
<td>Formoterol fumarate vs. placebo</td>
<td>24 weeks</td>
<td>All-cause mortality</td>
<td>GOLD A: 318</td>
<td>1/205 (0.5%)</td>
<td>0/113 (0%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>SUMMIT Vestbo, 2016\textsuperscript{16} Crim, 2017\textsuperscript{52}</td>
<td>Vilanterol vs. placebo</td>
<td>1.8 years (Median)</td>
<td>All-cause mortality</td>
<td>8229</td>
<td>265/4118 (6.4%)</td>
<td>275/4111 (6.7%)</td>
<td>HR: 0.96 (95% CI, 0.81 to 1.14)</td>
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<td></td>
<td>Annual rate of moderate/severe exacerbations</td>
<td>8229</td>
<td>0.31</td>
<td>0.35</td>
<td>Percent reduction: 10% (95% CI, 2% to 18%)</td>
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<td></td>
<td></td>
<td>Annual rate of hospitalized exacerbation</td>
<td>8229</td>
<td>0.06</td>
<td>0.07</td>
<td>Percent reduction: 20% (95% CI, 5% to 32%)</td>
</tr>
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<td></td>
<td></td>
<td>Composite CVD endpoint\textsuperscript{†}</td>
<td>8229</td>
<td>180/4118 (4.4%)</td>
<td>173/4111 (4.2%)</td>
<td>HR: 0.99 (95% CI, 0.80 to 1.22)</td>
</tr>
<tr>
<td>LABA/ICS</td>
<td>SUMMIT Vestbo, 2016\textsuperscript{16} Crim, 2017\textsuperscript{52}</td>
<td>Fluticasone furoate/vilanterol vs. placebo</td>
<td>1.8 years (Median)</td>
<td>All-cause mortality</td>
<td>8232</td>
<td>246/4121 (6.0%)</td>
<td>275/4111 (6.7%)</td>
<td>HR: 0.88 (95% CI, 0.74 to 1.04)</td>
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<td></td>
<td></td>
<td>Annual rate of moderate/severe exacerbations</td>
<td>8232</td>
<td>0.25</td>
<td>0.35</td>
<td>Percent reduction: 29% (95% CI, 22% to 35%)</td>
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<td></td>
<td></td>
<td>Annual rate of hospitalized exacerbation</td>
<td>8232</td>
<td>0.05</td>
<td>0.07</td>
<td>Percent reduction: 27% (95% CI, 13% to 39%)</td>
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<td></td>
<td></td>
<td></td>
<td>Composite CVD endpoint\textsuperscript{†}</td>
<td>8232</td>
<td>174/4121 (4.2%)</td>
<td>173/4111 (4.2%)</td>
<td>HR: 0.93 (95% CI, 0.75 to 1.14)</td>
</tr>
<tr>
<td>LAMA</td>
<td>UPLIFT Decramer, 2009\textsuperscript{16} Tashkin, 2012\textsuperscript{16} Tashkin,</td>
<td>Tiotropium bromide vs. placebo</td>
<td>48 months</td>
<td>Clinically important deterioration\textsuperscript{‡}</td>
<td>Stage II: 2,603</td>
<td>1053/1310 (80.4%)</td>
<td>1122/1293 (86.8%)</td>
<td>HR: 0.70 (95% CI, 0.65, 0.77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exacerbations\textsuperscript{§}</td>
<td>Stage II: 2,739</td>
<td>824/1384 (59.5%)</td>
<td>882/1355 (65.1%)</td>
<td>HR: 0.82 (95% CI, 0.75 to 0.90)</td>
</tr>
</tbody>
</table>
## Table 9. Key Question 2 Results: Outcomes for Included RCTs of Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Study, year</th>
<th>Treatment Comparison</th>
<th>Followup</th>
<th>Outcome</th>
<th>N analyzed</th>
<th>IG Events*</th>
<th>CG Events*</th>
<th>IG vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2008⁷⁴ Rabe, 2020⁸³ Halpin, 2015⁸⁴</td>
<td>FEV₁≥60%: NR (1210 randomized)</td>
<td>2008</td>
<td>GOLD category A: 357</td>
<td>91/188 (48.4%)</td>
<td>92/169 (54.4%)</td>
<td>RR: 0.64 (95% CI, 0.47 to 0.89)</td>
<td>HR: 0.77 (95% CI, 0.58 to 1.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinically meaningful deterioration in SGRQ†</td>
<td>2008</td>
<td>Stage II: 2,603</td>
<td>487/1310 (37.2%)</td>
<td>594/1293 (45.9%)</td>
<td>RR: 0.71 (0.63, 0.80)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PINNACLE Martinez, 2020⁷¹</td>
<td>Glycopyrrolate vs. placebo</td>
<td>24 weeks</td>
<td>All-cause mortality</td>
<td>GOLD A: 308</td>
<td>0/195 (0%)</td>
<td>0/113 (0%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>LAMA/ LABA PINNACLE Martinez, 2020⁷¹</td>
<td>Glycopyrrolate/formoterol fumarate vs. placebo</td>
<td>24 weeks</td>
<td>All-cause mortality</td>
<td>GOLD A: 330</td>
<td>0/217 (0%)</td>
<td>0/113 (0%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

* Number of events or event rate
† Includes MI, unstable angina, stroke, TIA, sudden death, procedural death, other cardiovascular death
‡ SGRQ increase ≥4 units, trough FEV₁ decline ≥100mL, moderate/severe exacerbation
§ Increase/new onset >1 respiratory symptom for ≥ 3 days requiring antibiotic and/or systemic steroid
ǁ Time to first exacerbation
¶ SGRQ increase ≥4 units

**Abbreviations:** CG = control group; CI = confidence interval; CVD = cardiovascular disease; FEV₁ = 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

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study</th>
<th>Treatment comparison</th>
<th>Outcome</th>
<th>Followup</th>
<th>N analyzed</th>
<th>IG Events</th>
<th>CG Events</th>
<th>IG vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-management</td>
<td>Bischoff, 2012&quot;66</td>
<td>Tailored self-management intervention vs. usual care</td>
<td>Exacerbation*</td>
<td>52 weeks</td>
<td>101</td>
<td>Rate per patient: 2.83</td>
<td>Rate per patient: 2.73</td>
<td>RR: 1.10 (95% CI, 0.86 to 1.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weeks 52-104</td>
<td></td>
<td>101</td>
<td>Rate per patient: 2.17</td>
<td>Rate per patient: 2.17</td>
<td>RR: 1.16 (95% CI, 0.81 to 1.67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-tailored self-management intervention vs. usual care</td>
<td>Exacerbation*</td>
<td>52 weeks</td>
<td>103</td>
<td>Rate per patient: 3.25</td>
<td>Rate per patient: 2.73</td>
<td>RR: 1.25 (95% CI, 0.98 to 1.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weeks 52-104</td>
<td></td>
<td>103</td>
<td>Rate per patient: 2.38</td>
<td>Rate per patient: 2.17</td>
<td>RR: 1.15 (95% CI, 0.80 to 1.65)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jolly, 2018&quot;88</td>
<td>Phone-based self-management intervention vs. printed information</td>
<td>Hospital admissions</td>
<td>26 weeks</td>
<td>531</td>
<td>Mean (SD): 0.07 (0.3)</td>
<td>Mean (SD): 0.06 (0.3)</td>
<td>IRR: 0.86 (95% CI, 0.45 to 1.62), p=0.64</td>
</tr>
<tr>
<td></td>
<td>PSM COPD</td>
<td></td>
<td></td>
<td>52 weeks</td>
<td>Mean (SD): 0.06 (0.3)</td>
<td>Mean (SD): 0.06 (0.3)</td>
<td>IRR: 0.90 (95% CI, 0.39 to 2.09), p=0.81</td>
<td></td>
</tr>
<tr>
<td>Moy, 2016&quot;85</td>
<td>Taking Healthy Steps</td>
<td>Web-based exercise intervention vs. pedometer only</td>
<td>Exacerbation or pneumonia</td>
<td>52 weeks</td>
<td>328</td>
<td>35/154 (22.7%)</td>
<td>15/84 (18%)</td>
<td>OR: 1.4 (95% CI, 0.7 to 2.8), p=0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospitalization</td>
<td></td>
<td>52 weeks</td>
<td>328</td>
<td>36/154 (23.4%)</td>
<td>14/84 (17%)</td>
<td>OR: 1.6 (95% CI, 0.8 to 3.2), p=0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emergency room visit</td>
<td></td>
<td>52 weeks</td>
<td>328</td>
<td>46/154 (29.9%)</td>
<td>20/84 (24%)</td>
<td>OR: 1.4 (95% CI, 0.8 to 2.6), p=0.27</td>
</tr>
<tr>
<td>Wan, 2020&quot;77</td>
<td>ESC</td>
<td>Web-based exercise intervention vs. pedometer only</td>
<td>Acute exacerbation§</td>
<td>65 weeks</td>
<td>109</td>
<td>NR</td>
<td>NR</td>
<td>RR: 0.51 (0.31 to 0.85)†</td>
</tr>
<tr>
<td>Supervised-exercise or pulmonary rehabilitation</td>
<td>Roman, 2013&quot;73</td>
<td>PR with maintenance program vs. usual care</td>
<td>Hospitalized for exacerbation</td>
<td>52 weeks</td>
<td>43</td>
<td>3/24 (12.5%)</td>
<td>3/19 (15.8%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary care visit for exacerbation</td>
<td></td>
<td>52 weeks</td>
<td>43</td>
<td>7/24 (30.3%)</td>
<td>9/19 (42.8%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospitalized for exacerbation</td>
<td></td>
<td>52 weeks</td>
<td>41</td>
<td>5/22 (22.7%)</td>
<td>3/19 (15.8%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary care visit for exacerbation</td>
<td></td>
<td>52 weeks</td>
<td>41</td>
<td>7/22 (35.0%)</td>
<td>9/19 (42.8%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* 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)
† While overall admissions were not significant, intervention participants reported lower doctor and pharmacist consultations, but higher all cause emergency department visits
§ No differences across any utilization measure
‡ New or increased respiratory symptoms with ≥2 the following criteria: increased cough, sputum, wheezing, dyspnea, or chest tightness for ≥3 days requiring antibiotics or new/increased systemic steroid use
¶ Favors intervention group

**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>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study</th>
<th>Treatment comparison</th>
<th>Followup</th>
<th>Outcome measure</th>
<th>N analyzed</th>
<th>IG: % with MCID</th>
<th>CG: % with MCID</th>
<th>Effect estimate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-management</td>
<td>Bischoff, 2012^66</td>
<td>Tailored self-management intervention vs. usual care</td>
<td>104 weeks</td>
<td>CRQ</td>
<td>110</td>
<td>NR</td>
<td>NR</td>
<td>-0.22 (95% CI, -0.49 to 0.042)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-tailored self-management intervention vs. usual care</td>
<td>104 weeks</td>
<td>CRQ</td>
<td>110</td>
<td>13/46 (28%)</td>
<td>8/44 (18%)</td>
<td>OR (MCID): 1.44 (95% CI, 0.61 to 3.38), Difference in change: 0.16 (95% CI, -0.11 to 0.42)</td>
</tr>
<tr>
<td>Jolly, 2018^46</td>
<td>PSM COPD</td>
<td>Phone-based self-management intervention vs. printed information</td>
<td>26 weeks</td>
<td>EQ-5D</td>
<td>516</td>
<td>NR</td>
<td>NR</td>
<td>0.01 (95% CI, -0.01 to 0.03), p=0.30</td>
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<tr>
<td></td>
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<td></td>
<td>52 weeks</td>
<td>SGRQ</td>
<td>459</td>
<td>NR</td>
<td>NR</td>
<td>-0.3 (95% CI, -2.3 to 1.7), p=0.76</td>
</tr>
<tr>
<td>Moy, 2016^45</td>
<td>Taking Healthy Steps</td>
<td>Web-based exercise intervention vs. pedometer only</td>
<td>52 weeks</td>
<td>SGRQ</td>
<td>238</td>
<td>NR</td>
<td>NR</td>
<td>0.01 (95% CI, -0.01 to 0.03), p=0.38</td>
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<td>-1.3 (95% CI, -3.6 to 0.9), p=0.23</td>
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<tr>
<td>Nyberg, 2019^72</td>
<td></td>
<td>Web-based self-management intervention vs. pedometer</td>
<td>52 weeks</td>
<td>CAT</td>
<td>83</td>
<td>NR</td>
<td>NR</td>
<td>Beta-coefficient: -1.1 (95% CI, -2.2 to 4.3), p=0.521</td>
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<td></td>
<td></td>
<td>EQ-5D</td>
<td>83</td>
<td>NR</td>
<td>NR</td>
<td>Beta-coefficient: 0.02 (95% CI, -0.03 to 0.07), p=0.980</td>
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<tr>
<td>Voncken-Brewster, 2015^76</td>
<td>MasterYourBreath</td>
<td>Web-based self-management intervention vs. usual care</td>
<td>26 weeks</td>
<td>CCQ</td>
<td>1307</td>
<td>NR</td>
<td>NR</td>
<td>Beta-coefficient: -0.03 (95% CI, -0.07 to 0.01), p=0.134</td>
</tr>
<tr>
<td>Wan, 2020^77</td>
<td>ESC</td>
<td>Web-based exercise intervention vs. pedometer only</td>
<td>52 weeks</td>
<td>SGRQ</td>
<td>109</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Weldam, 2017</td>
<td>COPD-GRIP</td>
<td>In-person self-management intervention vs usual care</td>
<td>39 weeks</td>
<td>CCQ</td>
<td>199</td>
<td>16/100 (15.7%)</td>
<td>13/99 (12.9%)</td>
<td>OR (MCID): NS, Difference in change: 0.04 (95% CI, -0.09 to 0.17), p=0.197</td>
</tr>
<tr>
<td>Exercise only</td>
<td>Altenburg, 2015^65</td>
<td>Lifestyle/exercise counseling vs usual care</td>
<td>65 weeks</td>
<td>CCQ</td>
<td>38</td>
<td>NR</td>
<td>NR</td>
<td>p=0.536</td>
</tr>
<tr>
<td></td>
<td>COACH</td>
<td></td>
<td></td>
<td>CRQ</td>
<td>38</td>
<td>NR</td>
<td>NR</td>
<td>p=0.278</td>
</tr>
<tr>
<td>Supervised exercise or pulmonary rehabilitation</td>
<td>Fastenau, 2020^77</td>
<td>Supervised exercise vs. low intensity exercise</td>
<td>26 weeks</td>
<td>CCQ</td>
<td>67</td>
<td>NR</td>
<td>NR</td>
<td>-0.09 (95% CI, -0.4 to 0.2), p=0.549</td>
</tr>
<tr>
<td>Liang, 2019^69</td>
<td>RADICALS</td>
<td>Lifestyle counseling plus home PR vs. usual care</td>
<td>26 weeks</td>
<td>CAT</td>
<td>208</td>
<td>NR</td>
<td>NR</td>
<td>0.66 (95% CI, -1.98 to 3.30), p=0.61</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>SGRQ</td>
<td>204</td>
<td>NR</td>
<td>NR</td>
<td>2.45 (95% CI, -0.89 to 5.79), p=0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52 weeks</td>
<td>CAT</td>
<td>189</td>
<td>NR</td>
<td>NR</td>
<td>0.86 (95% CI, -2.02 to 3.74), p=0.55</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>SGRQ</td>
<td>185</td>
<td>47/105 (44.8%)</td>
<td>38/90 (42.2%)</td>
<td>2.21 (95% CI, -2.86 to 7.28), p=0.38</td>
</tr>
<tr>
<td>Roman, 2013^73</td>
<td>PR with maintenance program vs. usual care</td>
<td>52 weeks</td>
<td>CRQ</td>
<td>36</td>
<td>NR</td>
<td>NR</td>
<td>NS for any subscale (total score NR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PR vs. usual care</td>
<td></td>
<td>52 weeks</td>
<td>CRQ</td>
<td>31</td>
<td>NR</td>
<td>NR</td>
<td>NS for any subscale (total score NR)</td>
</tr>
<tr>
<td>Intervention type</td>
<td>Author, Year Study</td>
<td>Treatment comparison</td>
<td>Followup</td>
<td>Outcome measure</td>
<td>N analyzed</td>
<td>IG: % with MCID</td>
<td>CG: % with MCID</td>
<td>Effect estimate*</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------</td>
<td>-----------------------------------------------------------</td>
<td>----------</td>
<td>-----------------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Clinician education only</td>
<td>Markun, 2018⁷⁰</td>
<td>Clinician training vs. usual care</td>
<td>52 weeks</td>
<td>CAT</td>
<td>216</td>
<td>NR</td>
<td>NR</td>
<td>-1.1 (95% CI, -3.3 to 1.1), p=0.32</td>
</tr>
<tr>
<td></td>
<td>Zwar, 2016⁷⁰</td>
<td>Clinician training vs. written information</td>
<td>52 weeks</td>
<td>CAT</td>
<td>222</td>
<td>NR</td>
<td>NR</td>
<td>LSM change: -0.20 (95% CI, -1.53 to 1.12), 0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAT</td>
<td></td>
<td></td>
<td></td>
<td>LSM change: -0.21 (95% CI, -2.55 to 2.14), 0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SGRQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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

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

*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 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

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study</th>
<th>Treatment comparison</th>
<th>Followup</th>
<th>Outcome measure</th>
<th>N analyzed</th>
<th>IG vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-management</td>
<td>Jolly, 2018&lt;sup&gt;64&lt;/sup&gt; PSM COPD</td>
<td>Phone-based self-management intervention vs. printed information</td>
<td>26 weeks</td>
<td>MET minutes a week (IPAQ)</td>
<td>506</td>
<td>Total self-reported physical activity, walking, moderate, and vigorous intensity activity were all significantly higher in the intervention arm at 6 months</td>
</tr>
<tr>
<td></td>
<td>Moy, 2016&lt;sup&gt;65&lt;/sup&gt; Taking Healthy Steps</td>
<td>Web-based exercise intervention vs. pedometer only</td>
<td>52 weeks</td>
<td>MET minutes a week (IPAQ)</td>
<td>482</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Nyberg, 2019&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Web-based self-management intervention vs. pedometer</td>
<td>52 weeks</td>
<td>Average daily step count</td>
<td>328</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Voncken-Brewster, 2015&lt;sup&gt;76&lt;/sup&gt; MasterYourBreath</td>
<td>Web-based self-management intervention vs. usual care</td>
<td>26 weeks</td>
<td>MET minutes a week (IPAQ-SF)</td>
<td>1,307</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Wan, 2020&lt;sup&gt;77&lt;/sup&gt; ESC</td>
<td>Web-based exercise intervention vs. pedometer only</td>
<td>26 weeks</td>
<td>Average daily step count</td>
<td>87</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52 weeks</td>
<td>Average daily step count</td>
<td>75</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise only</td>
<td>Altenburg, 2015&lt;sup&gt;65&lt;/sup&gt; COACH</td>
<td>Lifestyle/exercise counseling vs usual care</td>
<td>65 weeks</td>
<td>6MWD</td>
<td>38</td>
<td>Mean difference: NR, p=0.313&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Supervised exercise or pulmonary rehabilitation</td>
<td>Fastenau, 2020&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Supervised exercise vs. low intensity exercise</td>
<td>26 weeks</td>
<td>6MWD</td>
<td>67</td>
<td>Mean difference: 20.1 (95% CI: -6.5 to 46.7)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Roman, 2013&lt;sup&gt;73&lt;/sup&gt;</td>
<td>PR with maintenance program vs. usual care</td>
<td>52 weeks</td>
<td>6MWD</td>
<td>36</td>
<td>Mean difference in change: -13.5 (95%: -55.5 to 28.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PR vs. usual care</td>
<td>52 weeks</td>
<td>6MWD</td>
<td>31</td>
<td>Mean difference in change: -12.9 (95%: -56.7 to 30.7)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Intervention type</th>
<th>Author, Year Study</th>
<th>Intervention comparison</th>
<th>Followup</th>
<th>Outcome</th>
<th>N analyzed</th>
<th>IG</th>
<th>CG</th>
<th>IG vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-management</td>
<td>Jolly, 2018&lt;sup&gt;66&lt;/sup&gt; PSM COPD</td>
<td>Phone-based self-management intervention vs. printed information</td>
<td>26 weeks</td>
<td>Smoking cessation</td>
<td>114</td>
<td>14/64 (22%)</td>
<td>9/50 (18%)</td>
<td>P=0.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52 weeks</td>
<td>Smoking cessation</td>
<td>106</td>
<td>7/54 (13%)</td>
<td>13/52 (25%)</td>
<td>P=0.11</td>
</tr>
<tr>
<td></td>
<td>Voncken-Brewster, 2015&lt;sup&gt;76&lt;/sup&gt; MasterYourBreath</td>
<td>Web-based self-management intervention vs. usual care</td>
<td>26 weeks</td>
<td>7-day point prevalence abstinence</td>
<td>341</td>
<td>NR</td>
<td>NR</td>
<td>OR=1.06 (95% CI: 0.43 to 2.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24-hour point prevalence of abstinence</td>
<td>341</td>
<td>NR</td>
<td>NR</td>
<td>OR=0.72 (95% CI: 0.33 to 1.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Continued abstinence&lt;sup&gt;*&lt;/sup&gt;</td>
<td>341</td>
<td>NR</td>
<td>NR</td>
<td>OR=0.98 (95% CI: 0.37 to 2.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prolonged abstinence&lt;sup&gt;†&lt;/sup&gt;</td>
<td>341</td>
<td>NR</td>
<td>NR</td>
<td>OR=0.86 (95% CI: 0.33 to 2.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tobacco consumption</td>
<td>341</td>
<td>NR</td>
<td>NR</td>
<td>Beta-coefficient =0.11 (95% CI: -1.61 to 1.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intention to quit smoking</td>
<td>341</td>
<td>NR</td>
<td>NR</td>
<td>Beta-coefficient =-0.03 (95% CI: -0.32 to 0.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Number of quit attempts</td>
<td>341</td>
<td>NR</td>
<td>NR</td>
<td>Beta-coefficient=-0.38 (95% CI: -1.11 to 0.69)</td>
</tr>
<tr>
<td>Clinician education only</td>
<td>Zwar, 2016&lt;sup&gt;78&lt;/sup&gt; PELICAN</td>
<td>Clinician training vs. written information</td>
<td>52 weeks</td>
<td>Number of current smokers</td>
<td>222</td>
<td>28/126 (22%)</td>
<td>25/96 (26%)</td>
<td>OR: 0.92 (95% CI: 0.44 to 1.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vaccinated for influenza</td>
<td>222</td>
<td>91/126 (73%)</td>
<td>54/96 (57%)</td>
<td>OR: 2.31 (95% CI: 1.06 to 5.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vaccinated for pneumococcus</td>
<td>222</td>
<td>53/126 (48%)</td>
<td>36/96 (38%)</td>
<td>OR: 1.54 (95% CI: 0.86 to 2.71)</td>
</tr>
</tbody>
</table>

<sup>*</sup> Not smoked at all since last quit date
<sup>†</sup> Not smoked in two weeks since last quit date
<sup>‡</sup> Reports Ex-SRES: Exercise self efficacy (NS) and step counts (NS)
<sup>§</sup> 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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Study, year</th>
<th>Treatment Comparison</th>
<th>Followup</th>
<th>Outcome</th>
<th>N analyzed</th>
<th>IG Events</th>
<th>CG Events</th>
<th>IG vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>SUMMIT Vestbo, 2016</td>
<td>Fluticasone furoate vs. placebo</td>
<td>1.8 years (median)</td>
<td>Adverse events</td>
<td>8288</td>
<td>2820/4157 (68%)</td>
<td>2782/4131 (67%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Crim, 2017</td>
<td></td>
<td></td>
<td>Serious adverse events</td>
<td>8288</td>
<td>929/4157 (22%)</td>
<td>918/4131 (22%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatal adverse events</td>
<td>8288</td>
<td>183/4157 (4%)</td>
<td>192/4131 (5%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medication discontinuation due to adverse event</td>
<td>8288</td>
<td>367/4157 (9%)</td>
<td>397/4131 (10%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>8288</td>
<td>228/4157 (5.5%)</td>
<td>214/4131 (5.2%)</td>
<td>HR: 1.035 (95% CI, 0.859 to 1.247), p=0.716</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Severe pneumonia</td>
<td>8288</td>
<td>146/4157 (3.5%)</td>
<td>127/4131 (3.1%)</td>
<td>HR: 1.17 (95% CI, 0.880 to 1.416), p=0.364</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatal pneumonia</td>
<td>8288</td>
<td>10/4157 (0.2%)</td>
<td>9/4131 (0/2%)</td>
<td>HR: 1.079 (95% CI, 0.438 to 2.657), p=0.868</td>
</tr>
<tr>
<td>LABA</td>
<td>PINNACLE Vestbo, 2020</td>
<td>Formoterol fumarate vs. placebo</td>
<td>24 weeks</td>
<td>Serious adverse events</td>
<td>318</td>
<td>15/205 (7.3%)</td>
<td>7/113 (6.2%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Martinez</td>
<td></td>
<td></td>
<td>Serious adverse events related to study treatment*</td>
<td>318</td>
<td>0/205 (0%)</td>
<td>1/113 (0.9%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment related adverse events leading to early discontinuation</td>
<td>318</td>
<td>7/205 (3.4%)</td>
<td>8/113 (7.1%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>SUMMIT Vestbo, 2016</td>
<td>Vilanterol vs. placebo</td>
<td>1.8 years (median)</td>
<td>Adverse events</td>
<td>8271</td>
<td>2809/4140 (68%)</td>
<td>2782/4131 (67%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Crim, 2017</td>
<td></td>
<td></td>
<td>Serious adverse events</td>
<td>8271</td>
<td>972/4140 (23%)</td>
<td>918/4131 (22%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatal adverse events</td>
<td>8271</td>
<td>198/4140 (4%)</td>
<td>192/4131 (5%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medication discontinuation due to adverse event</td>
<td>8271</td>
<td>370/4140 (9%)</td>
<td>397/4131 (10%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>8271</td>
<td>163/4140 (3.9%)</td>
<td>214/4131 (5.2%)</td>
<td>HR: 0.722 (95% CI, 0.589 to 0.886), p=0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Severe pneumonia</td>
<td>8271</td>
<td>104/4140 (2.5%)</td>
<td>127/4131 (3.1%)</td>
<td>HR: 0.778 (95% CI, 0.600 to 1.008), p=0.057</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatal pneumonia</td>
<td>8271</td>
<td>6/4140 (0.1%)</td>
<td>9/4131 (0/2%)</td>
<td>HR: 0.632 (95% CI, 0.225 to 1.777), p=0.384</td>
</tr>
<tr>
<td>LABA/ICS</td>
<td>SUMMIT Vestbo, 2016</td>
<td>Fluticasone furoate/vilanterol vs. placebo</td>
<td>1.8 years (median)</td>
<td>Adverse events</td>
<td>8271</td>
<td>2780/4140 (67%)</td>
<td>2782/4131 (67%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Crim, 2017</td>
<td></td>
<td></td>
<td>Serious adverse events</td>
<td>8271</td>
<td>961/4140 (23%)</td>
<td>918/4131 (22%)</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table 15. Key Question 3 Results: Adverse Events for Included RCTs of Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Study, year</th>
<th>Treatment Comparison</th>
<th>Followup</th>
<th>Outcome</th>
<th>N analyzed</th>
<th>IG Events</th>
<th>CG Events</th>
<th>IG vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatal adverse events</td>
<td>8271</td>
<td>182/4140 (4%)</td>
<td>192/4131 (5%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medication discontinuation due to adverse event</td>
<td>8271</td>
<td>342/4140 (8%)</td>
<td>397/4131 (10%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>8271</td>
<td>237/4140 (5.7%)</td>
<td>214/4131 (5.2%)</td>
<td>HR: 1.038 (95% CI, 0.863 to 1.249), p=0.693</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Severe pneumonia</td>
<td>8271</td>
<td>140/4140 (3.4%)</td>
<td>127/4131 (3.1%)</td>
<td>HR: 1.022 (95% CI, 0.804 to 1.300), p=0.858</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatal pneumonia</td>
<td>8271</td>
<td>13/4140 (0.3%)</td>
<td>9/4131 (0.2%)</td>
<td>HR: 1.330 (95% CI, 0.567 to 3.117), p=0.512</td>
</tr>
<tr>
<td>LAMA</td>
<td>UPLIFT</td>
<td>Tiotropium bromide vs. placebo</td>
<td>48 months</td>
<td>Adverse events leading to discontinuation</td>
<td>Stage II subset: 2,739</td>
<td>235/1384 (17.0%)</td>
<td>241/1355 (17.8%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Decramer</td>
<td></td>
<td></td>
<td>FEV1≥60% subset: 1210</td>
<td>98/632 (15.5%)</td>
<td>88/578 (15.2%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200968</td>
<td></td>
<td></td>
<td>Fatal Adverse event</td>
<td>Category A: 357</td>
<td>13/188 (6.9%)</td>
<td>11/169 (6.5%)</td>
<td>RR: 1.03 (95% CI, 0.46 to 2.29)</td>
</tr>
<tr>
<td></td>
<td>Tashkin,</td>
<td></td>
<td></td>
<td>Fatal major cardiac events</td>
<td>Category A: 357</td>
<td>4/188 (2.1%)</td>
<td>12/169 (7.1%)</td>
<td>RR: 0.79 (95% CI, 0.35 to 1.78)</td>
</tr>
<tr>
<td></td>
<td>201267</td>
<td></td>
<td></td>
<td>Major adverse cardiac event</td>
<td>Category A: 357</td>
<td>11/188 (5.9%)</td>
<td>3/169 (1.8%)</td>
<td>RR: 1.16 (95% CI, 0.26 to 5.18)</td>
</tr>
<tr>
<td></td>
<td>Tashkin,</td>
<td></td>
<td></td>
<td>Glycopyrrolate vs. placebo</td>
<td>24 weeks</td>
<td>Serious adverse events related to study treatment</td>
<td>308</td>
<td>7/195 (3.6%)</td>
</tr>
<tr>
<td></td>
<td>200874</td>
<td></td>
<td></td>
<td>Serious adverse events related to study treatment</td>
<td>308</td>
<td>3/195 (1.5%)</td>
<td>1/113 (0.9%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Rabe,</td>
<td></td>
<td></td>
<td>Treatment related adverse events leading to early discontinuation</td>
<td>308</td>
<td>9/195 (4.6%)</td>
<td>8/113 (7.1%)</td>
<td>NR</td>
</tr>
<tr>
<td>PINNACLE</td>
<td>Martinez,</td>
<td></td>
<td>24 weeks</td>
<td>Glycopyrrolate/ formoterol fumarate vs. placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>202071</td>
<td></td>
<td></td>
<td>Serious adverse events</td>
<td>330</td>
<td>16/217 (7.4%)</td>
<td>7/113 (6.2%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serious adverse events related to study treatment</td>
<td>330</td>
<td>4/217 (1.8%)</td>
<td>1/113 (0.9%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment related adverse events leading to early discontinuation</td>
<td>330</td>
<td>12/217 (5.5%)</td>
<td>8/113 (7.1%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

* Adjudicated by investigator prior to unblinding

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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Study, year Quality</th>
<th>Study design Country, years</th>
<th>Population description</th>
<th>Outcome</th>
<th>N analyzed Follow-up</th>
<th>IG vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA or LAMA</td>
<td>Wang, 2018&lt;sup&gt;1&lt;/sup&gt; Fair</td>
<td>Nested case-control Taiwan, 2007-2011</td>
<td>LABA-LAMA naïve patients; 71.4 years (mean); 31.1% female; mean FEV&lt;sub&gt;1&lt;/sub&gt; NR</td>
<td>Risk of cardiovascular disease</td>
<td>N=37,719 cases; N=146,139 controls</td>
<td>LABA new use N=520 (1.4%) cases N=1186 (0.8%) controls Adjusted OR= 1.50 (95% CI: 1.35 to 1.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean 2.0 years</td>
<td></td>
<td>LABA prevalent use N=962 (2.6%) cases N=3795 (2.6%) controls Adjusted OR= 0.91 (95% CI: 0.85 to 0.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LAMA new use N=190 (0.5%) cases N=463 (0.3%) controls Adjusted OR= 1.52 (95% CI: 1.28 to 1.80)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LAMA prevalent use N=458 (1.2%) cases N=3795 (1.4%) controls Adjusted OR= 0.88 (95% CI: 0.79 to 0.98)</td>
<td></td>
</tr>
<tr>
<td>ICS</td>
<td>Price, 2019&lt;sup&gt;40&lt;/sup&gt; Fair</td>
<td>Cohort UK, 1990-2015</td>
<td>Mean age 68-71 years; 38-41% female; 55-74% stage 1/2; 63-66% GOLD class A/B</td>
<td>Diabetes onset (ICS vs. LABA initiation)</td>
<td>N = 17,970 (Category A/B subset: N = 9,923)</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 3.7-5.6 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes progression (ICS vs. LABA initiation)</td>
<td>N = 804 (Category A/B subset: N = 492)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 3.7-5.6 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Osteoporosis onset (ICS vs. LABA initiation)</td>
<td>N = 19,898 (Category A/B subset: N = 11,057)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 3.7-5.6 years</td>
<td></td>
</tr>
</tbody>
</table>

**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*

<table>
<thead>
<tr>
<th>KQ1: Effectiveness of screening</th>
<th>Evidence summary in 2016</th>
<th>New evidence findings</th>
<th>Limitations of new evidence</th>
<th>Consistency of new evidence with prior evidence findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No trials evaluated the effectiveness of screening or active case finding for COPD on patient health outcomes (i.e., COPD morbidity, mortality, HRQoL).</td>
<td>No published or ongoing trials identified.</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

| KQ2: Treatment benefits in screen relevant populations | Overall, the included treatment evidence (14 trials) 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., FEV1 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 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 or recommender preventive | Overall, the included evidence (5 studies) did not demonstrate a benefit for the incremental value of adding spirometry to smoking cessation. And no studies evaluated spirometry or the | Based on 3 included non-pharmacologic intervention trials and 1 additional comparative study looking at receipt of spirometry results (or ‘lung age’), detection of COPD did not increase smoking cessation. One trial evaluating clinician limited evidence with varying study designs evaluating the benefit of screening for COPD on the uptake of preventive services. | Generally consistent for no consistent benefit of spirometry or screening for COPD on smoking cessation. Benefits were only observed in one trial that has not yet been reproduced. Still no |

*New evidence findings evaluated spirometry or the inclusion of COPD diagnosis on a COPD screening process result to a presumed or known diagnosis of COPD does not increase smoking cessation.*

Screening for Chronic Obstructive Pulmonary Disease 61 Kaiser Permanente EPC
Table 17. Summary of Targeted Evidence Update in the Context of the Prior Systematic Review to Support the 2016 USPSTF Screening for COPD Recommendation*

<table>
<thead>
<tr>
<th>Services</th>
<th>Evidence summary in 2016</th>
<th>New evidence findings</th>
<th>Limitations of new evidence</th>
<th>Consistency of new evidence with prior evidence findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>incremental benefit of having a diagnosis of COPD on vaccination uptake.</td>
<td>education demonstrated an increase in the uptake of influenza vaccination.</td>
<td></td>
<td>comparative studies demonstrating the incremental benefit of spirometry or identification of COPD on uptake of recommended vaccinations or lung cancer screening.</td>
</tr>
</tbody>
</table>

* 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; FEV₁ = 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

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Country</th>
<th>N Randomized</th>
<th>Population</th>
<th>Treatment Comparison</th>
<th>Followup</th>
<th>Smoking abstinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotz, 2009&lt;sup&gt;108&lt;/sup&gt;, 126-128</td>
<td>Netherlands</td>
<td>296</td>
<td>Smokers aged 35-70 years; ≥1 respiratory symptom and mild or moderate COPD</td>
<td>Smoking cessation support with or without discussion of spirometry</td>
<td>52 weeks</td>
<td>Adjusted OR: 0.88 (95% CI, 0.38 to 2.03)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>McClure, 2009&lt;sup&gt;110, 129, 130&lt;/sup&gt;</td>
<td>US</td>
<td>542</td>
<td>Smokers aged ≥18 years</td>
<td>Smoking cessation support with spirometry results vs. smoking cessation support and “lung age”&lt;sup&gt;†&lt;/sup&gt;</td>
<td>52 weeks</td>
<td>30-day abstinence: OR: 0.77 (95% CI NR); p=0.34&lt;sup&gt;‡&lt;/sup&gt; 7-day abstinence: OR: 0.86 (95% CI NR); p=0.38&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parkes, 2008&lt;sup&gt;111&lt;/sup&gt;</td>
<td>UK</td>
<td>561</td>
<td>Smokers aged ≥35 years</td>
<td>Smoking cessation support with spirometry results vs. smoking cessation support and “lung age”&lt;sup&gt;§&lt;/sup&gt;</td>
<td>52 weeks</td>
<td>Between group difference: 7.2% (95% CI: 2.2% to 12.1%)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risser, 1990&lt;sup&gt;112&lt;/sup&gt;</td>
<td>US</td>
<td>90</td>
<td>Smokers in VA Demonstration Project</td>
<td>Smoking cessation support with or without discussion of spirometry</td>
<td>52 weeks</td>
<td>IG: 20.0%, CG 6.7%, p=0.06&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ronaldson, 2018&lt;sup&gt;114&lt;/sup&gt;</td>
<td>UK</td>
<td>674</td>
<td>Smokers aged ≥35 years</td>
<td>Lung function testing and COPD case finding vs waitlist control</td>
<td>24 weeks</td>
<td>Adjusted OR: 1.00 (95% CI, 0.57 to 1.77)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sippel, 1999&lt;sup&gt;113&lt;/sup&gt;</td>
<td>US</td>
<td>205</td>
<td>Smokers aged ≥18</td>
<td>Smoking cessation support with or without discussion of spirometry</td>
<td>39 weeks</td>
<td>Adjusted OR: 0.6 (95% CI, 0.2 to 1.4)&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Biochemically validated smoking cessation
† Calculated using method Morris and Temple method<sup>131</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  Bronchospirometry/
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.
Appendix A. Detailed Methods

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 as topic/ or randomized controlled clinical 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.
Appendix A. Detailed Methods

66 Brovana.ti,ab.
67 Formoterol.ti,ab.
68 Foradil.ti,ab.
69 Indacaterol.ti,ab.
70 breezhaler.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 (inha$ 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$.ti,ab.
110 Accuhaler.ti,ab.
111 Turbohaler.ti,ab.
112 Diskhaler.ti,ab.
113 Nebul?$er$.ti,ab.
Appendix A. Detailed Methods

Receptors, Interleukin-8B/((CXCR2 or interleukin 8B or IL8B or IL-8B) adj3 (antagonis$ or receptor$)).ti,ab.
CXC chemokine receptor 2.ti,ab.
(AZD5069 or AZD-5069).ti,ab.
(MK-7123 or MK7123 or Navarixin or SCH-527123).ti,ab.
(Danirixin or GSK1325756 or GSK-1325756).ti,ab.
(Elubrixin or SB-656933 or SB656933).ti,ab.
(SX-682 or SX682).ti,ab.
nonpharmacologic intervention$.ti,ab.
non pharmacologic intervention$.ti,ab.
"Delivery of Health Care, Integrated"/
Patient Care Management/
(Case management or Integrated care or Care coordination or coordinated care).ti,ab.
Counseling/
Directive Counseling/
Health Promotion/
Self-Management/
Risk Reduction Behavior/
health behavior/
Health Education/
Health Promotion/
Patient Education as Topic/
Healthy lifestyle/
counsel$.ti,ab.
(advice or advise or consultation$).ti,ab.
(behavior adj2 (therap$ or chang$ or modification$ or improv$)).ti,ab.
(monitoring adj1 (patient$ or activity or health)).ti,ab.
(set$ adj2 goal$).ti,ab.
action plan$.ti,ab.
(assessment adj5 feedback).ti,ab.
support planning.ti,ab.
risk factor management.ti,ab.
(lifestyle or lifestyle).ti,ab.
motivation$.ti,ab.
health coach$.ti,ab.
health behavior$.ti,ab.
health education.ti,ab.
education$.program$.ti,ab.
patient education.ti,ab.
self management$.ti,ab.
(self adj (model or plan)).ti,ab.
(promotion adj3 (health or exercise$ or physical activity$ or weight loss)).ti,ab.
Smoking cessation/
"Tobacco Use Cessation"/
Smoking Prevention/
((smoke$ or cigarette$) adj10 (cessation or quit$ or stop$ or abstain$ or abstinence)).ti,ab.
Diet, Reducing/ or nutrition therapy/ or nutritional support/
Appendix A. Detailed Methods

162 Feeding behavior/
163 Healthy diet/
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/
Appendix A. Detailed Methods

210 Heart Failure/
211 Heart Arrest/
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$.ti,ab.
219 constipation$.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 hematoma$.ti,ab.
225 ((oral or oropharyngeal) adj candidiasis) or moniliasis).ti,ab.
226 ((low or decrease$) 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 arrhythmia$.ti,ab.
235 tachycardia$.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 cardiomyopathy$.ti,ab.
240 (heart adj (failure$ 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 bronchospiromet*):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 (behavior* 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 behavior*: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 management*:ti,ab,kw
#104 (promotion NEAR/3 (health or exercise* or physical NEXT activity* or weight NEXT loss)):ti,ab,kw
#105 ((smoke* 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 (exercise* or physical NEXT activity*):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

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Populations</strong></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>KQ 1: Patients with diagnosed COPD or other respiratory conditions; patients with identified alpha-1 antitrypsin deficiency; pregnant women</td>
</tr>
<tr>
<td>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</td>
<td>KQs 2, 3: Patients with severe or very severe COPD; pregnant women; patients with identified alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>All KQs: Inpatient settings</td>
</tr>
<tr>
<td>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 (&gt;0.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>KQ 1: Testing used for disease monitoring or management, pulmonary imaging</td>
</tr>
<tr>
<td>KQ 1: Any screening method including prebronchodilator screening spirometry, questionnaires or risk assessment tools; peak flow meter; confirmatory post-bronchodilator spirometry</td>
<td>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</td>
</tr>
<tr>
<td>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)</td>
<td></td>
</tr>
<tr>
<td><strong>Comparisons</strong></td>
<td>All KQs: Active comparator</td>
</tr>
<tr>
<td>All KQs: Usual care; placebo; no screening/treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>KQs 1, 2: Change in FEV1</td>
</tr>
<tr>
<td>KQs 1, 2: All-cause mortality, disease specific mortality, COPD-related morbidity; HRQoL at ≥6 months followup</td>
<td>KQs 1, 2: Nonrandomized studies including cohort studies, case-control studies, case series</td>
</tr>
<tr>
<td>KQ 3: Serious adverse events requiring unexpected or unwanted medical attention and/or resulting in death (e.g., requiring hospitalization)</td>
<td></td>
</tr>
<tr>
<td><strong>Study Designs</strong></td>
<td></td>
</tr>
<tr>
<td>KQs 1, 2: RCT</td>
<td>KQs 1, 2: RCTs included for KQ2, large registry studies of drug safety</td>
</tr>
<tr>
<td>KQ 3: RCTs included for KQ2, large registry studies of drug safety</td>
<td></td>
</tr>
<tr>
<td><strong>Study Quality</strong></td>
<td>All KQs: Poor-quality</td>
</tr>
<tr>
<td>All KQs: Good- &amp; fair-quality</td>
<td>All KQs: Non-English studies</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
</tr>
<tr>
<td>All KQs: English</td>
<td></td>
</tr>
</tbody>
</table>

*Based on the GOLD criteria COPD classifications
†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; FEV1 = 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*

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Adapted Quality Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods³</td>
<td><strong>Bias arising in the randomization process or due to confounding</strong>&lt;br&gt;- Valid random assignment/random sequence generation method used&lt;br&gt;- Allocation concealed&lt;br&gt;- Balance in baseline characteristics&lt;br&gt;<strong>Bias in selecting participants into the study</strong>&lt;br&gt;- Controlled Clinical Trial only: No evidence of biased selection of sample&lt;br&gt;<strong>Bias due to departures from intended interventions</strong>&lt;br&gt;- Fidelity to the intervention protocol&lt;br&gt;- Low risk of contamination between groups&lt;br&gt;- Participants were analyzed as originally allocated&lt;br&gt;<strong>Bias from missing data</strong>&lt;br&gt;- No, or minimal, post-randomization exclusions&lt;br&gt;- Outcome data are reasonably complete and comparable between groups&lt;br&gt;- Reasons for missing data are similar across groups&lt;br&gt;- Missing data are unlikely to bias results&lt;br&gt;<strong>Bias in measurement of outcomes</strong>&lt;br&gt;- Blinding of outcome assessors&lt;br&gt;- Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups&lt;br&gt;- No evidence of inferential statistics&lt;br&gt;<strong>Bias in reporting results selectively</strong>&lt;br&gt;- No evidence that the measures, analyses, or subgroup analyses are selectively reported</td>
</tr>
<tr>
<td>Registry studies, adapted from the Newcastle-Ottawa Scale⁶⁰</td>
<td><strong>Does the cohort appear to be valid?</strong>&lt;br&gt;- Is the cohort representative of the average-risk patient?&lt;br&gt;- Did the study adjust for prognostic variables?&lt;br&gt;- Can we be confident in the assessment of the presence or absence of prognostic factors?&lt;br&gt;- Can we be confident in the assessment of outcomes?</td>
</tr>
</tbody>
</table>

* 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 reviewer.
Number of citations identified through key question literature database search: 19,354

Number of citations identified through other sources (e.g., reference lists, experts): 69

Number of citations screened after exclusion of duplicates: 6387

Number of citations excluded at title and abstract stage: 6158

Number of full-text articles assessed for eligibility for Key Questions 1, 2, and 3: 229

Articles excluded for Key Question 1: 229
Relevance: 219
Setting: 1
Population: 0
Quality: 0
Study design: 0
Intervention: 0
Comparator: 0
Outcomes: 1
Non-English: 2
Publication type: 6

Articles excluded for Key Question 2: 201
Relevance: 24
Setting: 1
Population: 76
Quality: 1
Study design: 75
Intervention: 3
Comparator: 12
Outcomes: 1
Non-English: 9
Publication type: 6

Articles excluded for Key Question 3: 209
Relevance: 2
Setting: 1
Population: 39
Quality: 1
Study design: 0
Intervention: 3
Comparator: 0
Outcomes: 155
Non-English: 2
Publication type: 6

Included for Key Question 1: 0 studies (0 publications)

Included for Key Question 2: 16 studies (28 publications)

Included for Key Question 3: 8 studies (20 publications)

Total number of included studies: 18 studies (30 publications)*

*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)


Appendix C. Included Studies List

### Excluded Studies List

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


4. 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


9. Bender, Bg, Make, Bj, et al. Enhancing physical activity in patients with chronic obstructive pulmonary disease (COPD)
through a program of patient selected goals. Am J Respir Crit Care Med. 191(Meeting Abstracts): A2458. 2015. KQ1E1, KQ2E5, KQ3E8


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


Appendix D. Excluded Studies List


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


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):
Appendix D. Excluded Studies List

66-74. 2017. **KQ1E1, KQ2E3a, KQ3E8**


60. Farmer, A, Williams, V, et al. Self-management support using an Internet-
Appendix D. Excluded Studies List

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


Appendix D. Excluded Studies List


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


88. Jackson, Be, Coultas, D, et al. Benefits of a lifestyle physical activity intervention for COPD are limited to patients with moderate impairment. Am J Respir Crit Care Med. 191(Meeting Abstracts): A4448. 2015. KQ1E10, KQ2E10, KQ3E10


93. Kalter-Leibovici, O, Benderly, M, et al. Disease Management plus Recommended Care versus Recommended Care Alone for Ambulatory Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 197(12): 1565-1574. 2018. KQ1E1, KQ2E3a, KQ3E8

94. Karapolat, H, Atasever, A, et al. Do the benefits gained using a short-term pulmonary rehabilitation program remain in COPD patients after participation?. Lung. 185(4): 221-5. 2007. KQ1E1, KQ2E5, KQ3E8


98. Kerwin, EM, Murray, L, et al. Clinically Important Deterioration Among Patients with Chronic Obstructive Pulmonary Disease (COPD) Treated with Nebulized Glycopyrrolate: A Post Hoc Analysis of Pooled Data from Two


105. Lazaar, AL, Miller, BE, et al. CXCR2 antagonist for patients with chronic obstructive pulmonary disease with chronic mucus hypersecretion: a phase 2b trial. Respir Res. 21(1): 149. 2020. KQ1E1, KQ2E3a, KQ3E3a

106. Lazaar, AL, Miller, BE, et al. Effect of the CXCR2 antagonist danirixin on symptoms and health status in COPD. Eur Respir J. 52(4): 10. 2018. KQ1E1, KQ2E3a, KQ3E3a


Appendix D. Excluded Studies List


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Appendix D. Excluded Studies List

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Appendix D. Excluded Studies List

severity and age; pooled analysis of GOLDEN 3 and GOLDEN 4. International Journal of Copd. 14, 27-37. 2019. KQ1E1, KQ2E5, KQ3E8


139. Polkey, MI, Qiu, ZH, et al. Tai Chi and Pulmonary Rehabilitation Compared for Treatment-Naive Patients With COPD: A Randomized Controlled Trial. Chest. 153(5): 1116-1124. 2018. KQ1E1, KQ2E5, KQ3E8

140. Pradella, CO, Belmonte, GM, et al. Home-Based Pulmonary Rehabilitation for Subjects With COPD: A Randomized Study. Respir Care. 60(4): 526-32. 2015. KQ1E1, KQ2E5, KQ3E8


146. Rice, KL, Dewan, N, et al. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med. 182(7): 890-6. 2010. KQ1E1, KQ2E3a, KQ3E8

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Appendix D. Excluded Studies List


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


Appendix D. Excluded Studies List


164. Smith, JA. The Effect of Aclidinium on Symptoms Including Cough in COPD: a Phase IV, Double-Blind, Placebo-Controlled, Parallel-Group Study. Am J Respir Crit Care Med. 2019. **KQ1E1, KQ2E5, KQ3E8**


Appendix D. Excluded Studies List

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184. Wang, CY, Lai, CC, et al. The association between inhaled corticosteroid and pneumonia in COPD patients: the improvement of patients' life quality with COPD in Taiwan (IMPACT) study. International Journal of Copd. 11. 2775-2783. 2016. **KQ1E1, KQ2E1, KQ3E3a**

185. Wang, L, Wu, K, et al. The Effects of Tai Chi on Lung Function, Exercise Capacity and Health Related Quality of
Appendix D. Excluded Studies List


192. Yudhawati, R, Rasjid Hs, M. Effect of yoga on FEV1, 6-minute walk distance (6-MWD) and quality of life in patients with COPD group B. Advances in Respiratory Medicine. 87(5): 261-268. 2019. KQ1E1, KQ2E5, KQ3E8


Appendix D. Excluded Studies List

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

<table>
<thead>
<tr>
<th>Study reference/ trial identifier</th>
<th>Study name</th>
<th>Location</th>
<th>Estimated N</th>
<th>Intervention Description</th>
<th>Relevant Outcomes</th>
<th>Status* Estimated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening or active case-finding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03583099</td>
<td>The CAPTURE Study: Validating a Unique COPD Case Finding Tool in Primary Care (Aim 3) (CAPTURE)</td>
<td>United States</td>
<td>5000</td>
<td>Physician education and use of CAPTURE tool (screening questionnaire and PEF measurement)</td>
<td>COPD symptoms scores, exacerbations, hospitalization, mortality</td>
<td>Ongoing Estimated completion: July, 2022</td>
</tr>
<tr>
<td>ISRCTN17942821</td>
<td>A self-management programme of activity coping and education - SPACE FOR COPD - in primary care: a pragmatic trial</td>
<td>United Kingdom</td>
<td>193</td>
<td>Group based self-management program (12 hours over 5 months)</td>
<td>Symptom status, exercise capacity, physical activity, QoL, mental health outcomes</td>
<td>Unknown* Estimated completion: 2017</td>
</tr>
<tr>
<td>NCT03654092</td>
<td>Home-based Exercise Training for COPD Patients (HOMEX-2)</td>
<td>Switzerland</td>
<td>120</td>
<td>Home-based exercise program</td>
<td>COPD symptoms, HRQoL, exacerbations</td>
<td>Recruiting Estimated completion: October 2020</td>
</tr>
<tr>
<td>ACTRN12618001091291</td>
<td>Mobile Health for Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>Australia</td>
<td>100</td>
<td>COPD mobile health app (education, action plan, monitoring symptoms, modification of risk factors)</td>
<td>COPD symptoms, QoL, lifestyle changes, exacerbations, hospital admissions</td>
<td>Ongoing Estimated completion: 2021</td>
</tr>
<tr>
<td>NCT03746873</td>
<td>Increase Level of Physical Activity and Decrease Use of Health Care for People With COPD (COPD)</td>
<td>Sweden</td>
<td>144</td>
<td>COPD Web: interactive web based tool to increase physical activity and appropriate self-management strategies</td>
<td>Pedometer with written information about physical activity</td>
<td>Recruiting Estimated completion: 2021</td>
</tr>
<tr>
<td>NCT04139200</td>
<td>Long-term Activity Coaching in Patients With COPD</td>
<td>Belgium</td>
<td>150</td>
<td>Long-term Activity Coaching in Patients With COPD</td>
<td>Health status, HRQoL, anxiety and depression</td>
<td>Ongoing Estimated completion: November 2021</td>
</tr>
</tbody>
</table>

*As of December 2020
†Contacted study author and no response