JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Chronic Obstructive Pulmonary Disease
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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

IMPORTANCE Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the US.

OBJECTIVE To conduct a targeted systematic review to update the evidence on the effectiveness of screening for COPD and the treatment of COPD to inform the US Preventive Services Task Force (USPSTF) update of the 2016 recommendation statement on COPD screening.

DATA SOURCES MEDLINE, the Cochrane Central Register of Controlled Trials, and CINAHL for relevant studies published between January 1, 2015, to January 22, 2021; surveillance through March 25, 2022.

STUDY SELECTION English-language studies of screening in individuals who do not recognize or report respiratory symptoms; studies of treatment in persons with mild or moderate, or minimally symptomatic, COPD.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently appraised the articles and extracted relevant data from fair- or good-quality studies; no quantitative synthesis was conducted.

MAIN OUTCOMES AND MEASURES COPD-related morbidity or mortality, measures of health-related quality of life, and adverse events.

RESULTS The review included no trials on the effectiveness of screening, 3 trials or analyses (n = 20 058) of pharmacologic treatment published since 2015, 13 trials (n = 3657) on nonpharmacologic interventions, and 2 large observational studies (n = 243 517) addressing the harms of pharmacologic treatment published since 2015. The results from the clinical trials of pharmacologic therapy are consistent with the previous review supporting the USPSTF that bronchodilators with or without inhaled corticosteroids can reduce COPD exacerbations and tiotropium can improve health-related quality of life in adults with moderate COPD. Overall, there was no consistent benefit observed for any type of nonpharmacologic intervention across a range of patient outcomes. 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 a long-acting muscarinic antagonist or long-acting beta agonist with the risk of a serious cardiovascular event in treatment-naïve patients and an association of inhaled corticosteroids use with the risk of developing diabetes.

CONCLUSIONS AND RELEVANCE The findings of this targeted evidence update are generally consistent with the findings of the previous systematic review supporting the 2016 USPSTF recommendation. Evidence of pharmacologic treatment was still largely limited to persons with moderate airflow obstruction, and there was no consistent benefit observed for a range of nonpharmacologic interventions in mild to moderate COPD or in minimally symptomatic persons with COPD.

Editorial page 1768

Multimedia

Related article page 1806 and JAMA Patient Page page 1831

Author Affiliations: Kaiser Permanente Evidence-based Practice Center, Center for Health Research, Kaiser Permanente, Portland, Oregon.

Corresponding Author: Jennifer S. Lin, MD, Kaiser Permanente Evidence-based Practice Center, Center for Health Research, Kaiser Permanente Northwest, 3800 N Interstate Ave, Portland, OR 97227 (jennifer.s.lin@kpchr.org).

JAMA. 2022;327(18):1812-1816. doi:10.1001/jama.2022.4708

Chronic obstructive pulmonary disease (COPD) is defined by a reduction in airflow that is not entirely reversible. COPD remains a leading cause of morbidity and mortality in the US.[1] The major risk factor for developing COPD and COPD mortality is exposure to smoke or fumes, notably direct or indirect exposure to cigarette smoke, and occupational or environmental exposures (eg, pollutants, wood smoke).[2] Many patients with COPD go undetected for multiple reasons, including underrecognition of mild symptoms (eg, dyspnea) or nonspecific symptoms (eg, fatigue). Screening or active case finding (ie, spirometry based on systematically assessing for symptoms, risk factors, or both) for COPD can detect persons otherwise not diagnosed as part of routine care; however, it is yet unclear if increased detection of persons with unrecognized symptoms improves patient health outcomes.

In 2008, and again in 2016, the US Preventive Services Task Force (USPSTF) issued a D recommendation against screening for COPD in asymptomatic adults (defined as individuals who do not recognize or report respiratory symptoms).[3] Although prior evidence demonstrated that screening could identify adults with COPD, there was no direct evidence that screening for COPD improved patient outcomes and limited treatment evidence to suggest a clinically meaningful benefit in persons considered to be most applicable to a screen-detected population.[4] Using the USPSTF reaffirmation process,[5] this targeted evidence update aimed to update the evidence on the effectiveness of screening for COPD and the treatment of COPD since 2015.

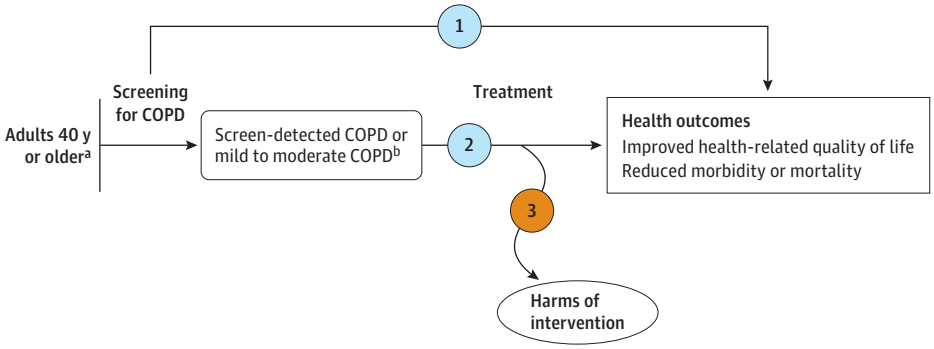
Methods

An analytic framework and 3 key questions (KQs) guided the evidence update (**Figure**). Detailed methods and results of this systematic review are available in the full evidence report.[6]

A literature search of MEDLINE, the Cochrane Central Register of Controlled Trials, and CINAHL was conducted from January 1, 2015, to January 22, 2021. Because the previous review did not include nonpharmacologic interventions, these searches were supplemented by examining reference lists of recent reviews and primary studies, and citations provided by experts, to identify major studies published prior to 2015. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. Since January 2021, ongoing surveillance to identify new studies that might affect the review conclusions or interpretation of the evidence was conducted using article alerts and targeted searches of journals with high impact factors. The last surveillance, conducted on March 25, 2022, identified no new studies that would meet inclusion criteria for this review.

To address KQ1 on the effectiveness of screening or risk-tailored screening (referred to as active case finding) for COPD on health outcomes, the review included randomized clinical trials of any screening method (eg, spirometry, questionnaire, or risk assessment followed by spirometry) in asymptomatic adults, adults who have symptoms undetected by the patient or clinician

Figure. Analytic Framework: Screening for Chronic Obstructive Pulmonary Disease



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?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate to interventions and outcomes. Further details are available from the USPSTF Procedure Manual. COPD indicates chronic obstructive pulmonary disease.

[a] Asymptomatic adults, adults who have physical symptoms undetected by the patient or the clinician (eg, mild dyspnea that goes unnoticed), or adults who have nonspecific symptoms (eg, sporadic sputum production or cough, fatigue) that have gone unrecognized as related to COPD.

[b] Mild (forced expiratory volume in 1 second [FEV_1] ≥80% predicted) to moderate (FEV_1 50%-79% predicted).

Table. Comparison of Foundational and New Evidence: Screening and Treatment for Chronic Obstructive Pulmonary Disease

	Evidence summary in 2016[4]	New evidence findings	Limitations of new evidence	Consistency of new evidence with foundational evidence and current understanding
Effectiveness of screening	No trials identified	No trials identified	NA	NA
Benefit of pharmacologic treatment	14 RCTs (n = 12 846) Evidence largely among individuals with moderate COPD Only consistent benefit observed was reduced COPD exacerbations with no consistent benefits in mortality, dyspnea, or health-related quality of life	3 RCTs (n = 20 058) Bronchodilators and inhaled corticosteroids can reduce COPD exacerbations in persons with moderate COPD In a small subgroup analyses from 1 trial (n = 357), LAMA (ie, tiotropium) reduced exacerbations in minimally symptomatic persons with moderate airflow obstruction	Limited evaluation of pharmacologic therapies in "screen-relevant" populations	Generally consistent for limited benefit of bronchodilators and inhaled corticosteroids for reduction in exacerbation outcomes Evidence is primarily in individuals with moderate COPD, leading to unclear wider applicability to screen-detected persons with COPD Signal for benefit of tiotropium on exacerbations in minimally symptomatic persons
Harms of pharmacologic treatment	8 RCTs (n = 10 368) Overall, limited data on serious harms reported in included treatment trials suggested no substantial serious adverse effects for most bronchodilators and inhaled corticosteroids	3 RCTs and 2 observational studies (n = 242 588) Initiation of a LAMA or LABA is associated with an increase in risk of serious cardiovascular events, and inhaled corticosteroids are associated with an increase in risk of developing diabetes	Harms not consistently reported in trials of pharmacologic interventions Treatment trials are limited in their ability to detect uncommon or longer-term harms	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 inhaled corticosteroids
Benefit of nonpharmacologic treatment	NA	13 trials (n = 3658) No consistent benefit for a range of nonpharmacologic interventions observed across multiple outcomes	Trials were generally small, had usual comparator groups in settings that may provide more care than typically received in the US, and/or had suboptimal uptake of the intervention	NA
Harms of nonpharmacologic treatment	NA	3 trials (n = 929) Self-management intervention trials did not demonstrate any serious harms	Harms not consistently reported in trials of nonpharmacologic interventions	NA

Abbreviations: COPD, chronic obstructive pulmonary disease; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; NA, not applicable; RCT, randomized clinical trial.

(eg, mild dyspnea that goes unnoticed), or adults who have nonspecific symptoms (eg, sporadic sputum production or cough, fatigue) that have gone unrecognized as related to COPD. To address KQ2 and KQ3 on the benefits and harms of treatment, studies conducted in persons with screen-detected COPD or adults with mild to moderate COPD defined by spirometry, low symptom burden, or both as defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were included.[7]

Two investigators independently evaluated articles that met inclusion criteria and summarized the data. Outcomes of interest included mortality, morbidity from COPD, measures of health-related quality of life, and adverse events. Given the limited number of pharmacologic trials and clinical heterogeneity in the nonpharmacologic trials, quantitative synthesis was not conducted.

Results

We screened 6387 titles and abstracts and 229 full-text articles. As in the previous review for the USPSTF,[4] no eligible trials were identified that directly examined the effectiveness of screening or active case finding for COPD on health outcomes (KQ1). Sixteen trials evaluating the treatment of mild to moderate, or minimally symptomatic, COPD were identified, including 3 trials (n = 20 058) published since 2015 evaluating pharmacologic therapy[8-10] and 13 trials (n = 3657) evaluating nonpharmacologic interventions (ie, self-management interventions, exercise counseling interventions, supervised exercise and pulmonary rehabilitation interventions, and clinician education interventions) (KQ2).[11-23] Two large observational studies (n = 243 517) published since 2015 addressed harms of pharmacologic treatment (KQ3).[24,25]

Three studies were identified since 2015 with newly published analyses of pharmacologic treatment in mild to moderate COPD, or in minimally symptomatic persons (ie, GOLD category A), since the 2016 review. Overall, the results from the clinical trials of pharmacologic therapy are consistent with the previous review's findings that bronchodilators with or without inhaled corticosteroids can reduce COPD exacerbations and tiotropium can improve health-related quality of life in adults with fairly symptomatic moderate COPD (**Table**).[8-10] The Understanding Potential Long-Term Impacts on Function With Tiotropium (UPLIFT) trial (n = 5993)[8] was included in the previous review but had 2 newly published post hoc subgroup analyses in adults with moderate COPD (stage II) (n = 2603)[26] and minimally symptomatic patients (GOLD category A) (n = 357).[27] The subgroup of individuals with minimal symptoms (ie, GOLD category A) found a reduction in exacerbations with tiotropium at 48 months.[27]

Thirteen trials evaluated nonpharmacologic interventions used in the management of mild to moderate, or minimally symptomatic (GOLD category A), COPD: 7 trials of self-management interventions,[11-17] 1 trial of exercise-only counseling,[18] 3 trials of

intensive supervised exercise or pulmonary rehabilitation,[19-21] and 2 trials of clinician education or training on COPD care.[22,23] Among these trials no consistent benefit was observed across a range of outcomes (ie, exacerbations, health-related quality of life, dyspnea, exercise or physical performance measures, mental health, smoking cessation) at 26 to 104 weeks (Table).

There was limited evidence on the harms of pharmacologic and nonpharmacologic interventions in the treatment of mild to moderate, or minimally symptomatic, COPD. None of the included trials that reported adverse effects found significant harms. In addition to the trial evidence, 2 large observational studies addressing harms of pharmacologic treatment demonstrated that initiation of a long-acting muscarinic antagonist or long-acting beta agonist may increase the risk of serious cardiovascular events in treatment-naïve patients[24] and that inhaled corticosteroids may increase the risk of developing diabetes (Table).[25]

Discussion

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. As in the previous review, no treatment studies were identified that were conducted in patients with screen-detected COPD, with evidence almost exclusively among individuals with moderate COPD. The only consistent benefit observed was reduced COPD exacerbations with no consistent benefits in mortality, dyspnea, or health-related quality of life. This review contained newly included evidence related to nonpharmacologic treatment. While no consistent benefit was seen among these trials 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. In addition, nonpharmacologic intervention and sharing spirometry results (or lung age) have not been found to improve smoking cessation, and data on the uptake of other preventive services (eg, vaccination, lung cancer screening) are limited.[6] In general, harms of pharmacologic and nonpharmacologic interventions were not consistently reported in treatment trials, although large observational studies suggest harms for the initiation of a long-acting muscarinic antagonist or long-acting beta-agonist and the longer-term use of inhaled corticosteroids in persons with COPD.

To date, there are still no completed studies evaluating the effectiveness of screening or active case finding for COPD on patient health outcomes. Currently, there is 1 cluster randomized clinical trial, COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE), of screening for COPD underway that will provide direct evidence for the effectiveness of screening for COPD in the US.[28] That trial evaluates screening with a 5-item questionnaire and peak flow measurement in persons aged 45 to 80 years 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.

Limitations

This review has several limitations. First, this targeted evidence update did not address the screening yield or screening accuracy of various screening or active case-finding approaches. Second, to approximate a screen-detected population, studies of treatment benefits or harms were limited to those in persons with mild to moderate COPD or who were minimally symptomatic (based on GOLD criteria), or studies that reported subgroup analyses in these persons. Third, forced expiratory volume in 1 second was not an included outcome.

Conclusions

The findings of this targeted evidence update are generally consistent with the findings of the previous systematic review supporting the 2016 recommendation. Evidence of pharmacologic treatment was still largely limited to persons with moderate airflow obstruction, and there was no consistent benefit observed for a range of nonpharmacologic interventions in mild to moderate COPD or in minimally symptomatic persons with COPD.

ARTICLE INFORMATION

Accepted for Publication: March 14, 2022.

Author Contributions: Ms Webber and Dr Lin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Webber, Lin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Webber.
Critical revision of the manuscript for important intellectual content: All authors.
Obtained funding: Lin.
Administrative, technical, or material support: Webber, Thomas.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was funded under HHSA290201500007I, Task Order 9, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the US Preventive Services Task Force (USPSTF).

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We thank the following for their contributions to this project: the AHRQ staff; the US Preventive Services Task Force; and Melinda Davies, MAIS, and Jill Pope, BA (Kaiser Permanente Center for Health Research), for technical and editorial assistance. The USPSTF members, peer reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 3 content experts (Jerry Krishnan MD, PhD, University of Illinois Chicago; Richard Mularski, MD, MSHS, MCR, Kaiser Permanente Northwest; Barbara Yawn, MD, MSc, University of Minnesota) and 1 federal partner (Centers for Disease Control and Prevention). Comments were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

REFERENCES

1. Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease (COPD): data and statistics. Published 2021. Accessed September 15, 2021. https://www.cdc.gov/copd/data.html

2. Diaz-Guzman E, Mannino DM. Epidemiology and prevalence of chronic obstructive pulmonary disease. *Clin Chest Med*. 2014;35(1):7-16. doi:10.1016/j.ccm.2013.10.002

3. Siu AL, Bibbins-Domingo K, Grossman DC, et al; US Preventive Services Task Force (USPSTF). Screening for chronic obstructive pulmonary disease: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;315(13):1372-1377. doi:10.1001/jama.2016.2638

4. Guirguis-Blake JM, Senger CA, Webber EM, Mularski RA, Whitlock EP. Screening for chronic obstructive pulmonary disease: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;315(13):1378-1393. doi:10.1001/jama.2016.2654

5. US Preventive Services Task Force. US Preventive Services Task Force Procedure Manual. Published May 2021. Accessed March 15, 2022. https://www.uspreventiveservicestaskforce.org/uspstf/procedure-manual

6. Lin JS, Webber EM, Thomas RG. *Screening for Chronic Obstructive Pulmonary Disease: A Targeted Evidence Update for the US Preventive Services Task Force. Evidence Synthesis No. 215*. Agency for Healthcare Research and Quality; 2022. AHRQ publication 21-05287-EF-1.

7. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Published 2021. Accessed March 15, 2022. https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf

8. Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554. doi:10.1056/NEJMoa0805800

9. Vestbo J, Anderson JA, Brook RD, et al; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet*. 2016;387(10030):1817-1826. doi:10.1016/S0140-6736(16)30069-1

10. Martinez FJ, Rabe KF, Lipworth BJ, et al. Glycopyrrolate/formoterol fumarate metered dose inhaler improves lung function versus monotherapies in GOLD category A patients with COPD: pooled data from the phase III PINNACLE studies. *Int J Chron Obstruct Pulmon Dis*. 2020;15:99-106. doi:10.2147/COPD.S229794

11. Bischoff EW, Akkermans R, Bourbeau J, van Weel C, Vercoulen JH, Schermer TR. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. *BMJ*. 2012;345:e7642. doi:10.1136/bmj.e7642

12. Jolly K, Sidhu MS, Hewitt CA, et al. Self management of patients with mild COPD in primary care: randomised controlled trial. *BMJ*. 2018;361:k2241. doi:10.1136/bmj.k2241

13. Weldam SWM, Schuurmans MJ, Zanen P, Heijmans MJWM, Sachs APE, Lammers JJ. The effectiveness of a nurse-led illness perception intervention in COPD patients: a cluster randomised trial in primary care. *ERJ Open Res*. 2017;3(4):00115-2016. doi:10.1183/23120541.00115-2016

14. Nyberg A, Tistad M, Wadell K. Can the COPD web be used to promote self-management in patients with COPD in swedish primary care: a controlled pragmatic pilot trial with 3-month and 12-month follow-up. *Scand J Prim Health Care*. 2019;37(1):69-82. doi:10.1080/02813432.2019.1569415

15. Voncken-Brewster V, Tange H, de Vries H, Nagykaldi Z, Winkens B, van der Weijden T. A randomized controlled trial evaluating the effectiveness of a web-based, computer-tailored self-management intervention for people with or at risk for COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1061-1073. doi:10.2147/COPD.S81295

16. Wan ES, Kantorowski A, Polak M, et al. Long-term effects of web-based pedometer-mediated intervention on COPD exacerbations. *Respir Med*. 2020;162:105878. doi:10.1016/j.rmed.2020.105878

17. Moy ML, Martinez CH, Kadri R, et al. Long-term effects of an internet-mediated pedometer-based walking program for chronic obstructive pulmonary disease: randomized controlled trial. *J Med Internet Res*. 2016;18(8):e215. doi:10.2196/jmir.5622

18. Altenburg WA, ten Hacken NH, Bossenbroek L, Kerstjens HA, de Greef MH, Wempe JB. Short- and long-term effects of a physical activity counselling programme in COPD: a randomized controlled trial. *Respir Med*. 2015;109(1):112-121. doi:10.1016/j.rmed.2014.10.020

19. Fastenau A, van Schayck OC, Winkens B, Aretz K, Gosselink R, Muris JW. Effectiveness of an exercise training programme COPD in primary care: a randomized controlled trial. *Respir Med*. 2020;165:105943. doi:10.1016/j.rmed.2020.105943

20. Liang J, Abramson MJ, Russell G, et al. Interdisciplinary COPD intervention in primary care: a cluster randomised controlled trial. *Eur Respir J*. 2019;53(4):1801530. doi:10.1183/13993003.01530-2018

21. Román M, Larraz C, Gómez A, et al. Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomized controlled trial. *BMC Fam Pract*. 2013;14:21. doi:10.1186/1471-2296-14-21

22. Markun S, Rosemann T, Dalla-Lana K, Steurer-Stey C. Care in Chronic Obstructive Lung Disease (CAROL): a randomised trial in general practice. *Eur Resp J*. 2018;51(5):1701873. doi:10.1183/13993003.01873-2017

23. Zwar NA, Bunker JM, Reddel HK, et al. Early intervention for chronic obstructive pulmonary disease by practice nurse and GP teams: a cluster randomized trial. *Fam Pract*. 2016;33(6):663-670. doi:10.1093/fampra/cmw077

24. Wang MT, Liou JT, Lin CW, et al. Association of cardiovascular risk with inhaled long-acting bronchodilators in patients with chronic obstructive pulmonary disease: a nested case-control study. *JAMA Intern Med*. 2018;178(2):229-238. doi:10.1001/jamainternmed.2017.7720

25. Price DB, Voorham J, Brusselle G, et al. Inhaled corticosteroids in COPD and onset of type 2 diabetes and osteoporosis: matched cohort study. *NPJ Prim Care Respir Med*. 2019;29(1):38. doi:10.1038/s41533-019-0150-x

26. Rabe KF, Halpin DMG, Han MK, et al. Composite endpoints in COPD: clinically important deterioration in the UPLIFT trial. *Respir Res*. 2020;21(1):177. doi:10.1186/s12931-020-01431-y

27. Halpin DMG, Tashkin DP, Celli BR, Leimer I, Metzdorf N, Decramer M. Effect of tiotropium on outcomes in patients with COPD, categorized using the new GOLD grading system: results of the UPLIFT® randomized controlled trial. *Chronic Obstr Pulm Dis*. 2015;2(3):236-251. doi:10.15326/jcopdf.2.3.2014.0142

28. 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) validation in primary care study. *Chronic Obstr Pulm Dis*. 2021;8(1):60-75. doi:10.15326/jcopdf.2020.0155