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**Reducing Disease Exacerbation in Women with Confirmed COPD: A Systematic
Literature Review**

Jill Essay

School of Nursing Minnesota State Mankato

N695 Alternate Plan Paper

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Abstract

A systematic literature review was conducted to establish whether gender specific treatment exists for patients with Chronic Obstructive Pulmonary Disease (COPD), specifically, women with (COPD). The PICO question developed for this review is as follows: *In women with confirmed diagnoses of COPD, does gender-specific treatment, compared to standard treatment, impact the frequency of exacerbations?* Could the number of COPD exacerbations in women be reduced by incorporating interventions designed with (female) gender in mind? Four databases were included in the search: CINAHL, Pubmed, Medline, and Nursing and Allied Health. Articles included addressed gender differences in relation to the disease process, medication(s), or overall treatment. There were 16 articles selected for this review. This analysis found gender differences with regards to lung development, disease presentation, diagnosis, exacerbations, and prognosis. A definitive answer to the PICO question was not found from this systematic review, yet future research is warranted to determine whether gender differences to exist with regards to treatments/interventions in patients with COPD. Recommendations for practice, research, education, and policy are based on articles included within the review.

Keywords: Chronic obstructive pulmonary disease, COPD, women or female, gender differences, exacerbations

Reducing Disease Exacerbation in Women with Confirmed COPD: A Systematic Literature Review

Chronic obstructive pulmonary disease (COPD) is the third most common cause of death in the United States (US) (Guarascio et al., 2013). In 2010, the cost of COPD in the US was projected to be approximately \$50 billion, which includes \$20 billion in indirect costs and \$30 billion in direct health care expenditures (Guarascio et al., 2013). COPD is a progressive disease and the cost of treating this illness is not decreasing in the US, however, earlier diagnosis and medication advancements can add years to patient lives (Guarascio et al., 2013). COPD was previously considered a male dominant disease process, but current data reveals women with COPD now exceed men in hospitalization and death (Celli et al., 2010). Celli et al. (2010) designed a study a three-year study, -Toward a Revolution COPD (TORCH), to evaluate sex differences related to risk of death from COPD, TORCH results indicate women were 16 percent less likely to die from the disease, but when covariates such as body mass and airflow obstruction were corrected, the results between genders were equal. Data indicates that with each progressive stage of COPD, as defined in the GOLD guideline, the cost to treat patients increases (Guarascio et al., 2013). Patients with stage I COPD experienced the lowest direct cost of \$1681 per patient per year, stage II patients will incur \$5037 per patient per year, and those in stage III had the highest cost of care, \$10,812 per patient per year (Guarascio et al., 2013).

COPD varies in etiology. It is a progressive disease of airway obstruction caused by inflammation; which narrows airways, increases mucus production, and subsequently creates a cough; all of which can create dyspnea for the individual (Breyer et al., 2011). Primary risk

factors for COPD include cigarette smoking and biomass. The disease process included pulmonary and non-pulmonary manifestations, with dyspnea and cough as the most prevalent symptoms in patients with COPD (Breyer et al., 2011). After a diagnosis of COPD, a referral for pulmonary function testing to establish baseline spirometry values is a prudent next step (Breyer et al., 2011).

Early diagnosis is key in controlling and limiting progression of COPD; once thought to be impossible (Criner et al., 2019). Smoking cessation, vaccinations, supplemental oxygen for hypoxemic patients, and lung volume reduction surgery in selected patients all improve survival; smoking cessation also attenuates disease progression (Criner et al., 2019). Patients with COPD experience episodes of increased symptomology that may necessitate hospitalization and intense management of the illness at times (Criner et al., 2019). Secondary infections have their own symptoms and may worsen existing disease (Criner et al., 2019), further increasing risk for an exacerbation and need for hospitalization.

Emerging research suggests that women and men may progress differently through the disease process (Celli et al., 2011; Criner et al., 2019). Research up until this point has primarily focused on male with COPD (Grabicki et al., 2019) It is now recognized that COPD in women is a major healthcare problem worldwide (Cote & Chapman, 2009). This may be due to increasing rates of cigarette smoking in women, hazardous work environments, and/or wood smoke exposure. Women's airways are also smaller than men's and it is possible women require less of a caustic agent to damage their lungs or that the exposure to caustic agents is higher due to their smaller airways (Martinez et al., 2012). The burden of COPD among women continues to grow; the number of women dying from COPD in the US now exceeds that of men (Celli et al., 2010).

Clinical Question

The following PICO question was developed to guide the systematic review of the literature: *In women with confirmed diagnoses of COPD (P) does gender-specific treatment (I) compared to standard treatment (C) impact the frequency of exacerbations (O)?* The research question included a comparison group, as it was hypothesized that specific treatment by gender may offer better health-related quality of life (HRQoL) and disease management in women affected by COPD in addition to lessening the frequency and number of exacerbations.

Clinical Significance for Advanced Practice

Advanced practice providers (APP) readily see female patients with COPD in the primary care clinic setting. Recommending the best possible medication or treatment regimen for this subpopulation allows the opportunity to educate and facilitate a COPD care plan that will not only promote better HRQoL, but also fewer COPD exacerbations.

Methods

A systematic literature review was done to produce current articles regarding the PICO question cited above. Electronic databases were utilized to find relevant materials related to treatment of women with COPD, to evaluate whether gender-specific or standard treatment affected reduced symptoms of disease, and if those treatments decrease the number of exacerbations women experience. The primary focus of this review is whether or not there is a difference when gender is considered in the treatment of COPD.

Database

The databases searched for this review were the Cumulative Index of Nursing and Allied Health (CINAHL), PubMed, Medline, and Nursing and Allied Health. Restrictions added to the search were that articles had to be full text, printed in the English language, and peer reviewed.

The articles had to be published between the years 2010 and 2020 assuring currency of research.

The initial search results can be viewed in the Appendix, Table 1.

Abstraction Process

The abstraction process limited the key words to Chronic Obstructive Pulmonary Disease, COPD, women, treatment, exacerbations, gender differences, interventions, outcomes, and female. The initial search yielded 9071 articles (see Table 1 in the Appendix). Article criteria was further reduced based on the following words; Chronic Obstructive Pulmonary Disease, women or female, gender differences, and exacerbations. This brought the article total to 38.

Results can be viewed in the Appendix, Table 2.

Search Strategies

Thirty-eight articles were reviewed based on the abstract and content to decide if they fit the purpose of the literature review. They were excluded if they did not address the central themes related to gender comparison or female treatment related to COPD exacerbations. If a gender difference was noted in the article with regards to lung development, risk factors, testing, diagnosis, or treatment, the article was included in the analysis. Exclusion versus inclusions criteria and findings can be viewed in can be viewed in the Appendix, Table 3.

Literature Review Process

There were 16 articles included in this literature review. Research on COPD in females is relatively new. Previous research has focused on the male population. Similarities among the articles in the review suggest that differences do exist between genders with relation to COPD (Augusti et al., 2010; Breyer et al., 2011; Celli et al., 2011; Kohler et al., 2013, Martinez et al., 2012). Only one article clearly addressed the clinical question regarding gender and treatment and its effect on disease exacerbation (Celli et al., 2011). No research was found to support the

use of specific medication protocols or treatment plans for females with COPD (Celli et al., 2011) Several articles offer partial answers to the question and will help steer future research. Further data related to these articles can be found in the Appendix, Table 4.

Study Characteristics

Of the 16 studies researched, two were level I studies, one study was a level II study, twelve were level III studies, and one was a level IV study (see Table 4 in the Appendix). The level I studies consisted of two systematic reviews. The level II study looked at laboratory data for comparison. The level III studies consisted of trials, measurement comparison, trend comparison, straight-forward comparison, data review, cross-sectional study, randomized control study, and multiple regression analysis. The single level IV study utilized a multi-variate logistic regression model to identify proteins of interest (Kohler et al., 2012). The population samples included both men and women with COPD. All studies had more male participants than female participants. One study used veterans who had developed COPD and hospital admissions rates to assess for gender differences (Fuhrman et al., 2011). Only one of the studies, (Wedzicha et al., 2019) specifically addressed, medications as an intervention/treatment, and its effect related to gender. Wedzicha et al. (2019) did not find the results differed between genders with regard to medication used to treat COPD. The medication classes in this study were a combination inhaled long acting bronchodilator and corticosteroid.

Definitions:

Six-minute walk: The distance that is walked in a 6-minute period. There are predicted normal values for the six minute-walk based on age and sex. This screening test is predictive of functional status (Torres et al., 2011).

Biomass: Fumes related to household work, occupationally related, or woodsmoke (Cote & Chapman 2009).

Bronchoalveolar lavage cell proteome: A proteome obtained during a bronchoalveolar lavage (BAL). BAL is a lung fluid sample obtained via normal saline inserted into the lung and drawn out carrying lung fluid with it (Kohler et. al., 2013)

BODE index: An index that considers several criteria to estimate a survival rate in years. The criteria are FEV1 % of predicted, six-minute walk distance, mMRC dyspnea scale, and BMI (Cote & Chapman, 2009).

DOSE index: (D) dyspnea, (O) airflow obstruction, (S) current smoking status, (E) frequency of exacerbations in the past year (Wang et al., 2017).

FEV1: The amount of air a patient can expel from his/her lungs in one second. This maneuver is done during spirometry testing, also referred to as pulmonary function testing. This test produces a predicted value for a gender and age. The test assesses lung function based on what percent a patient scores in relation to the predicted lung function for age and gender. Lung function in those with COPD, elicits reduced scores, in relation to predicted FEV1 %. The guideline for a positive diagnosis of COPD is achieving a score of 80% (or less) of predicted. 80% of the predicted lung function would suggest mild disease; 50% to 79% suggests moderate disease, 30-49% suggests severe disease, and less than 30% is considered very severe or end stage disease (Cote & Chapman, 2009).

Lung Information Needs Questionnaire (LINQ). This instrument can be used as a baseline for establishing information needs/patient understanding of COPD and its treatment for comparison with future evaluations (Wakabayashi et al., 2019).

mMRC: Modified Medical Research Council Dyspnea scale is used to distinguish severity of dyspnea in respiratory illness (Cote & Chapman, 2009).

SGRQ: St. George's Respiratory Questionnaire is utilized in those with obstructive lung diseases. It measures disease impact on the patient's overall health, daily activities, and perceived well-being (Celli et al., 2011).

TORCH: Toward a Revolution in COPD Health. This was a 3-year study to determine sex differences in survival causes of death, and patient-centered outcomes in a 3-year period (Celli et al., 2011).

Results

Biomarkers

There are differences between men and women at a cellular level. Kohler et al. (2012) studied the gender differences of bronchoalveolar lavage cell proteome in COPD patients. Kohler et al. (2012) found there are changes that occur in female COPD patient's proteomes that do not occur in male patients proteomes. It was learned that these changes also do not happen in female non-smokers (Kohler et al., 2012). Kohler et al. (2012) demonstrated that there is a specific change in female smokers who develop COPD. The differences identified in these studies further support that gender differences exist in COPD phenotypes and diagnosis and treatment on the basis of gender warranting further investigation.

De Torres, et al. (2011) did a pilot study looking at biomarker levels in a cohort of COPD patients. Of these patients 80 were smokers without COPD (40 male and 40 female) and 152 were stable COPD patients (76 male and 76 female), with similar airflow obstruction at time of study. De Torres, et al. (2011) found there was statistical difference in level IL-6, IL16, and VEGF levels between women and men with COPD (de Torres et al., 2011). The researchers

acknowledge that this study needs to be replicated to further support or refute these preliminary findings.

Breyer et al. (2011) studied the role of leptin in relation to gender differences in COPD. They found women with COPD had an increase in leptin compared to men with COPD and healthy females without COPD. Leptin secretion increased with increasing fat mass to a greater extent in COPD women when compared with their male counterparts, supporting the hypothesis of gender-specific leptin metabolism in COPD (Breyer et al., 2011). It is unknown at this time if increased weight carries an increased risk of symptoms in COPD patients. What is known is significant: There is a change in leptin metabolism in women with COPD.

Factors Impacting Gender Response to COPD

Potential variable related to sex differences in tobacco susceptibility causing COPD include differences in metabolism, hormonal influences, lung anatomy, inhalation technique, or a dose exposure because women's lungs are smaller than men's (Criner et al. 2019). Wood smoke exposure is possible in homes that utilize wood as a heat source. It is known that cigarette smoking is the leading contributor of COPD causes (Criner et al., 2019). Airway hyper-responsiveness in men is associated with allergies and asthma, whereas airway hyper-responsiveness in women it is associated with smoking indicating that airways react differently in men and women (Criner et al., 2019). It is known that women with COPD are frequently initially misdiagnosed with asthma and not tested with spirometry until after their first hospitalization. Bade et al. (2019) suggest that prior to a hospitalization, women were less likely to have pulmonary function testing or be treated with antimuscarinic or combined long-acting bronchodilator/inhaled corticosteroid inhalers. This demonstrates the delay that happens in the

diagnosis of COPD and treatment in women. It is now recognized that early diagnosis is proven to slow disease progression (Bade et al., 2019).

Readmission is strongly influenced by comorbidities, suggesting that individualized and comprehensive case management may reduce readmission risk for women and men. (Bade et al., 2019) Cote et al. (2009) considered the unique findings of two separate COPD related studies conducted by Miravittles et al. (2006) and Chapman et al. (2001). These two studies, essentially equal on all accounts, were developed into cases for providers to review for purposes of making a COPD diagnosis. Women with COPD were diagnosed 11-16% less correctly than men with COPD by the participating providers. However, when spirometry was utilized in the given cases, the primary care providers (PCPs) were less likely to miss a diagnosis of COPD in both men and women.

Gender Effects of Medications Approved for COPD Treatment

A study by Wedzicha et al. (2019) reviewed the combination medication indacaterol/glycopyronium, which is a long-acting beta agonist (LABA) and an inhaled corticosteroid, and whether gender differences were found when taking this medication regularly. Although there were gender differences in baseline characteristics between men and women with COPD in the Wedzicha et al. (2019) study, indacaterol/glycopyronium demonstrated similar trends for exacerbation, prevention, and lung function improvement in men and women with moderate-to-very severe COPD. In addition to the above, Wedzicha et al. (2019), compared indacaterol/glycopyronium against the drug combination salmeterol/fluticasone, which is also a LABA/corticosteroid combination medication. Both of these medications are administered via a multi-dose inhaler. The indacaterol/glycopyronium dose was 110/50 ug once daily and the salmeterol/fluticasone dose was 50/500 twice daily. Although,

the prior medication combination would be more convenient, it didn't offer an advantage of improving COPD outcomes in women. (Wedzicha et al., 2019)

Barriers to Care/Education

Significant gender-related differences in the perception of COPD healthcare delivery exist, revealing an opportunity to better understand what influences attitudes and to improve care for both men and women with COPD (Martinez et al., 2012). Martinez et al. (2012) showed that women generally made less money, were diagnosed later, and felt they had a harder time reaching a provider to discuss COPD care needs. Based on questionnaire results, it appears that there is a gap in education for female patients (Martinez et al., 2012). This occurred even though the availability of physicians, rehabilitation services, and insurance were similar to that of men. Wakabayashi et al. (2019) explored gender differences in COPD knowledge utilizing the LINQ. They found that females displayed significantly higher information needs than men. No difference was seen between sexes on subjects of knowledge, medicine, smoking, and exercise domains; the gender difference involved knowledge about avoidance of disease exacerbation.

Disease State and Dyspnea Disconnect

The main theme throughout the articles in this review is that female patients report greater dyspnea than is expected for measured lung function. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) was a large multi-country, multi-patient study conducted in 46 centers. This study was designed to define COPD phenotypes and identify biomarkers to aid in the prediction of disease progression (Augusti, et al., 2010). The severity of airflow limitation in COPD patients was poorly related to exacerbation reported in the year prior to the study (Augusti et al., 2010). Celli et al. (2011) found that even when correcting for degree of airflow obstruction, women report more anxiety and depression,

worse symptoms, lower exercise capacity, more airway hyperresponsiveness, and worse HRQoL than men. This could be related to smaller airways and disease progression. Much less is known about any sex differences in mortality and the factors that may affect it in the patients with COPD (Celli et al., 2011).

Exacerbations and Hospitalizations Related to Exacerbations

Acute exacerbation of COPD (AE-COPD) are major events in the disease course, especially when they necessitate a hospitalization (Fuhrman et al., 2011). Grabicki et al. (2019) found that women had significantly more exacerbations than men. In fact, they observed that women experienced at least two to four more exacerbations in a two year interval compared to men who experienced exacerbations in the same time interval. Overall women have fewer comorbidities as a whole (Bade et al., 2019). Comorbidities can exacerbate COPD symptoms and in some cases cause a need for hospitalization. There is a correlation for both men and women regarding exacerbations, but it is slightly stronger for women (Fuhrman et al., 2011). Fuhrman et al. (2011) found in a French study that COPD exacerbations were increasing for women and follow illness trends such as influenza.

Prognosis of COPD

Prognosis is typically based on how well the treatment works for the patient, whether or not the patient quits smoking, and how effectively they are with self-management (Wang et al., 2017). The DOSE index is a good predictor of patient prognosis (Wang et al., 2017). Wang et al. (2017) conducted an exploratory study that demonstrated higher physical activity, higher BMI, and female sex were important factors for lowering the DOSE index, thereby offering ways that might improve the prognosis of patients with COPD.

Gaps in Literature

The primary gap with regards to gender-based COPD treatment currently is trialing medications head-to-head with specific care plans that are developed by patient gender. This is an area where further research is needed in order to impact the frequency and severity of COPD exacerbations and outcomes for women.

Discussion

This systematic literature review focuses on whether gender-specific versus standard treatment could reduce exacerbations in women with COPD. Over a five-year study period Grabicki et al. (2019) attempted to evaluate whether significant differences could be found between Polish women and men suffering from COPD, with regard to clinical presentation, pulmonary function test results, comorbidities, and prognosis. Grabicki et al. (2019) found gender differences existed for exacerbations, comorbidities and prognosis. Women had more exacerbations, less comorbidities on average (although a wider distribution of comorbidities), and worse prognosis with less cigarette exposure than their male counterparts (Criner et al., 2019). Agusti et al. (2010) found that when subjects of similar age, and gender were analyzed by BODE scores, females reported less smoking exposure and more exacerbations than their male counterparts. In stable COPD patients with similar airflow obstruction, there are gender differences in plasma biomarker levels and in the association between biomarker levels and important clinical or physiological variables (de Torres et al., 2011). de Torres et al. (2011) acknowledges that further research is needed beyond their pilot study to further validate their findings. de Torres et al. (2011) suggest their study can serve as a hypothesis for future research. Interestingly, in the de Torres et al. (2011) study, there was no difference in the plasma biomarker levels in smokers without COPD.

Women achieve peak lung function earlier than males (15 years versus 22 years) (Criner et al., 2019). This is of significance because women are more likely to develop COPD with less tobacco exposure than men, thus suggesting a developmental component difference in this disease (Criner et al., 2019). Potential causes of sex differences in tobacco susceptibility include differences in metabolism, hormonal influences, lung anatomy, inhalation technique, or a dose exposure because women's lungs are smaller than men's (Criner et al., 2019). Airway hyperactivity in men is associated with allergies and asthma, whereas in women it is associated with smoking; indicating airways react differently in men and women (Cote & Chapman, 2009). Women tend to report a lesser pack-year history than men diagnosed with COPD (Criner et al., 2019). While studies are varied on the subject of smoking, newer literature suggest women are more susceptible to the harmful effects of smoking (Criner et al., 2019), possibly due to anatomical structure. Women's smaller airways may expose them to a larger quantity the chemicals in cigarette smoke (Cote & Chapman 2009; Criner et al., 2019).

Women tend to be under-diagnosed with COPD (Ford et al., 2014). Use of spirometry testing reduces under-diagnosing and in many instances PCPs just fail to test (Cote & Chapman, 2009). It is harder to overlook an abnormal test result, especially when they align with a COPD diagnosis.

Currently there is limited research on gender-based treatment. Wedzicha et al. (2019) post-hoc analysis in the FLAME study, found IND/GLY did not out-perform SFC for exacerbation prevention in women with COPD, despite gender differences in baseline characteristics in lung function. Women reported greater improvement in quality of life with IND/GLY (Wedzicha et al., 2019), yet this assertion was not supported by decreased exacerbations or disease progression (Wedzicha et al., 2019). However, (Wedzicha et al., 2019)

found IND/GLY didn't worsen the disease. There appears to be a disconnect as women do not report the same symptom relief or increase in (HRQoL). This does not mean that men and women should be treated the same or different. There just isn't enough information to make this determination with what we currently know about this disease and its impact on female gender. Medication regimens are tailored based on disease characteristics and patient symptomology. Non-pharmacologic therapies such as pulmonary rehabilitation should be available to all patients with COPD. It has been shown that the efficacy of both oxygen therapy and exercise therapy may vary according to gender (Cote & Chapman 2009).

Women report more dyspnea and less frequency of cough and phlegm than men with same disease state (August et al., 2010). Common comorbidities experienced concurrently with COPD by women include heart disease, diabetes, stroke, anxiety, depression, obesity, osteoporosis, and arthritis (Augusti et al., 2010). While Augusti et al. (2010) could list differences in comorbidities it is unknown what causes the differences COPD symptoms in relation to them. It could encompass female anatomy, comorbidities, and/or possibly treatment effects. Breyer et al. (2011) discusses a study done by Ahonen et al. (2008) that demonstrated decreased plasma concentrations of the anti-inflammatory adiponectin in women and increased CRP in men that may contribute to symptom differences in the etiology of COPD between genders. This is why it is so important to further evaluate women and the various etiologies and effects of COPD has on their health and HRQoL.

When compared to men, women frequently use an emotion-focused coping strategy, a response characterized by such emotions as anxiety and depression (Martinez et al., 2012). Anxiety and depression may be contributing to the feeling dyspnea witnessed at increased rate in women in relation to the disease process. Martinez et al. (2012) found that as sources of disease

education for patients with COPD expand, women are now obtaining information about their disease from online support groups, and fewer women are obtaining disease information from their physician as compared to how men gain insights into and understanding COPD. This related to the women feeling that the diagnosis was initially delayed and that contact with their provider was difficult. This fact in itself creates potential for anxiety in a patient male or female.

When women are compared to men with the same state of disease and comorbidities, the BODE is a good indicator of mortality (Wang et al., 2017) The BODE index considers patient's body mass index, airflow obstruction (from spirometry testing), dyspnea, and exercise capacity (Wang et al., 2017). Wang et al. (2017) asserts, the DOSE index may be a better indicator for overall prognosis of COPD.

COPD is a chronic illness that is partially self-managed (Wakabayashi et al., 2019). For a patient to successfully manage COPD in the home setting and avoid the need for medical intervention (up to and including hospitalization), education is key (Wakabayashi et al., 2019). Patients need to have knowledge about disease management, who to contact during an exacerbation or crisis, and medical coverage. Despite reporting similar access to healthcare insurance, physicians, and pulmonary rehabilitation, more women than men reported insurance as a barrier to at least one aspect of their care (Martinez et al., 2012). Patients with early stage to mild COPD are not perceived as high risk and subsequently might not receive adequate self-management education, and this may explain why the total LINC score was correlated with FEV1, and percent predicted (Wakabayashi et al., 2019). Studies have found that women require more education about self-management (Martinez et al., 2012; Wakabayashi et al., 2019). This suggest that for female COPD patients, more exacerbations and emergency visits may occur due to a lack of education and that action plans might not be executed correctly (Wakabayashi et al.,

2019). Wakabayashi et al. (2019) findings demonstrate why it is important to routinely assess cognitive function of patients at appointments. It is necessary to ensure the capacity of the patient to utilize information given about disease, follow up, and requirements for self-management.

Strengths and Weaknesses Associated with Review Findings

The strength of the research is yet to be fully understood. Utilization of measurement tools and devices to gauge disease progression and dyspnea over time is a big first step. The main weakness is the inability to draw any concrete conclusion on how to treat women with COPD in regard to symptom management and/or exacerbations of the disease process. This is primarily due to a lack of studies to draw evidence from in which we should base our practice decisions. Repeated studies to confirm results and research involving gender specific studies will strengthen findings that then in turn can be used in the practice setting in the future.

Recommendations for Clinical Practice

The PCP should work in collaboration with a pulmonologist to manage female patients with COPD. Reviewing medications, controlling various comorbidities, providing vaccinations, and smoking cessation education and treatment if needed are the hallmarks of the PCP's role with this patient. The PCP should always review the level of dyspnea patients with COPD are experiencing along with their ability to manage tasks of daily living. Even with this single focus, the PCP may be able to assist this patient in avoiding AE-COPD.

Recommendations for Research

There is a need for repeat studies involving medications available for managing patients with COPD. This needed research should consider gender as a way to tailor medications and treatments to best serve the female population. Perhaps interventional research, such as ways to better communicate treatment options with female patients who are experiencing COPD/COPD

exacerbations, will increase knowledge surrounding disease process and ultimately improve outcomes and reduce exacerbations.

Recommendations for Education

PCPs should remain current regarding best practice related to females with COPD. Understanding how comorbidities affect the patient may assist in primary care appointments and help patient reduce AE-COPD. Patients need to know what to monitor in relation to COPD, proper administration of prescribed medications and treatments, how to treat symptoms of disease at home, when to call the PCP for assistance, and when they need to seek emergency care. These topics are a few key points to assist in successful disease management at home. Women require additional education to be successful with self-management (Martinez et al., 2012; Wakabayashi et al., 2019).

Recommendation for Policy

There should be further efforts to establish health policy once it is known and better understood how the role of gender impacts treatment of COPD. This review did not produce any QI measures. This is something that could be researched in a future review or study. Health policy should focus on issues surrounding readmission after exacerbations and reducing exacerbations overall.

Conclusion

This systematic literature review was able to discern several differences between genders in relationship to COPD. Unfortunately, the initial PICO question was not able to be answered by the research findings contained within this systematic review, however it was a productive start for this subject and additional research should be forthcoming. There is emerging evidence that COPD in women is increasing and will be a burden to the healthcare system going forward.

Women are more susceptible to developing COPD possibly due to the anatomy of their smaller airways or lungs being fully developed at the time they start smoking (usually around 15 years of age). Regardless of the reason, women require less exposure to cigarette smoke than men to develop COPD. Currently there is a lack of research on pharmacological and non-pharmacological treatment specifically for women. Due to this omission, the initial question asked in this systematic review cannot be answered but strongly advocates for a need for additional research. Women with COPD need more education about this disease to aid with their plan of care, the ability to self-manage, and avoid exacerbations. PCPs need to help manage comorbid conditions effectively as poor control of these conditions can lead to increased COPD symptoms and AE-COPD which can lead to the unfortunate outcome of hospitalization.

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- Wakabayashi, R., Motegi, T., & Kida, K. (2019, January). Gender differences in chronic obstructive pulmonary disease using the lung information needs questionnaire. *Sage Open Nursing, 5*.
- Wang, L., Tao, Y.-X., Dong, X.-Y., Zhang, Q., Zheng, H., Zheng, Y.-S., . . . Zhao, Y. (2017, February). Demographic, health behavioral, and self-management abilities associated with disease severity among patients with chronic obstructive pulmonary disease. *International Journal of Nursing Practice, 23*(1).
- Wedzicha, J. A., Singh, D., Tseligianni, I., Jenkins, C., Fucile, S., Fogel, R., . . . Kostikas, K. (2019, January 8). Treatment response to indacaterol/glycopyrronium versus salmeterol/fluticasone in exacerbating COPD patients by gender: a post-hoc analysis in the FLAME study. *Respiratory Research, 20*(1).
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Appendix

Table 1

Database Search Description

Database (or Search Engine)	Restrictions Added to Search	Dates Included in Database	General Subjects covered by Database
Cinahl	Full Text; English Language; Peer-reviewed	2010-2020	Literature of nursing, physical therapy, occupational therapy, nutrition, and dietetics, and other health-related professions
PubMed	Full Text; English Language; Peer-(Martinez, et al., 2012)reviewed	2010-2020	Life sciences, behavioral sciences, chemical sciences, and bioengineering
Medline	Full Text; English Language; Peer-reviewed	2010-2020	Medicine, nursing, pharmacy, dentistry, veterinary medicine, and health care
Nursing and Allied Health	Full Text; English Language; Peer-reviewed	2010-2020	Nursing, allied health, alternative and complementary medicine

Table 2*Data Abstraction Process*

Date of Search	Key Words	Results in Cinahl	Results in PubMed	Results in Medline	Results in Nursing and Allied Health
10/25/2020	COPD, women, and treatment	30	1413	62	7566
	COPD, exacerbations, and gender differences	6	150	10	2249
10/26/2020	COPD, exacerbations, interventions, and outcomes	41	2409	68	3776
11/22/2020	Chronic obstructive pulmonary disease, women or female, gender differences, and exacerbations	8	10	2	20

Table 3*Characteristics of literature included and excluded*

Reference	Included or Excluded and Document	Rationale
Agusti, A., Calverley, Peter M.A., Celli, B., Coxson, H. O., Edwards, L. D., Lomas, D. A., . . . Vestbo, J. (2010). Characteristics of COPD heterogeneity in the ECLIPSE cohort. <i>Respiratory Research</i> , 122-135.	Included	Some gender differences were also identified within this study
Al-kassimi, F. A., Abba, A. A., Al-hajjaj, M. S., Alhamad, E. H., Raddaoui, E., & al., e. (2011, June). Asthma masquerading as chronic obstructive pulmonary disease: A study of smokers. <i>Respiration</i> , 82(1), 19-27.	Excluded	Comparison here is between asthma and COPD.
Antoniades, N., Rochford, P., Pretto, J., Pierce, R., Gogler, J., Steinkrug, J., . . . McDonald, C. (2012, October 18). Pilot study of remote telmonitoring in COPD. <i>Telemedicine Journal and E-Health</i> , 18(8), 634-640.	Excluded	Lacked breakdown based on gender for management of disease.
Bade, B. C., DeRycke, E. C., Ramsey, C., Skanderson, M., Crothers, K., & al., e. (2019, June). Sex differences in veterans admitted to the hospital for chronic obstructive pulmonary disease. <i>Annals of the American Thoracic Society</i> , 16(6), 707-714.	Included	Objective of study is to determine risk factors for 30-day readmission among Veterans hospitalized for COPD exacerbations and how they differed by sex.

<p>Beeh, K., Glaab, T., Stowasser, S., Schmidt, H., Fabbri, L., RAbe, K., & Vogelmeier, C. (2013, October 29). Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. <i>Respiratory Research</i>, 14(1).</p>	Excluded	Focus here is on tiotropium and how frequent exacerbations affect disease outcome. Lacked gender differences.
<p>Bhatt, S. P., Washko, G. R., Hoffman, E. A., Newell, J. D., Bodduluri, S., & al., e. (2019, February 1). Imagining advances in chronic obstructive pulmonary Disease: Insights from the genetic epidemiology of chronic obstructive pulmonary disease (COPDGene) study. <i>American Journal of Respiratory and Critical Care Medicine</i>, 199(3), 286-301.</p>	Excluded	Focus is on imaging of disease and not gender-specifics.
<p>Boutou, A. K., Stanopoulos, L., Pitsiou, G. G., Kontakiotis, T., Kyriazia, G., & al., e. (2011, August). Anemia of chronic disease in chronic obstructive pulmonary disease: a case-control study of cardiopulmonary exercise responses. <i>Respiration</i>, 82(3), 237-245.</p>	Excluded	Not focused on women or gender differences in relationship to COPD
<p>Breyer, M.-K., Rutten, E. P., Vernooij, J. H., Spruit, M. A., Dentener, M. A., & al., e. (2011, July). Gender differences in the adipose secretome system in chronic obstructive pulmonary disease (COPD): a pivotal role of leptin. <i>Respiratory Medicine</i>, 105(7), 1046-1053.</p>	Included	Investigates gender related differences in the adipokine metabolism in relation to systemic inflammatory biomarkers in clinically stable subjects with COPD.
<p>Burtin, C., & Hebestreit, H. (2015, March). Rehabilitation in patients with chronic respiratory disease other than chronic obstructive disease: exercise and</p>	Excluded	Focus is on relationship of CF to COPD and not gender differences of COPD or females with COPD,

<p>physical activity interventions in cystic fibrosis and non-cystic fibrosis bronchiectasis. <i>Respiration</i>, 89(3), 181-189.</p>		
<p>Celli, B., Vestbo, J., Jenkins, C. R., Jones, P. W., Ferguson, G. T., & al., e. (2011, February 1). Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. <i>American Journal of Respiratory and Critical Care Medicine</i>, 183(3), 317-322.</p>	Included	<p>Little is known about survival and clinical prognostic factors in females with chronic obstructive pulmonary disease (COPD). The aim of the present study was to determine the survival difference between males and females with COPD and to compare the value of the different prognostic factors for the disease.</p>
<p>Criner, G. J., Martinez, F. J., Aaron, S., Agusti, A., Anzueto, A., & al., e. (2019, January). Current controversies in chronic obstructive disease. A report from the global initiative for chronic obstructive lung disease scientific committee. <i>Annals of the American Thoracic Society</i>, 16(1).</p>	Included	<p>Discussion on women being diagnosed more than previously. More likely to develop lung disease if a women smokes than a man who smokes. Raises the importance of having a plan for women diagnosed with disease.</p>
<p>de Torres, J. P., Casanove, C., Pinto-Plata, V., Varo, N., Restituto, P., & al., e. (2009, January). Gender differences in plasma biomarker levels in a cohort of COPD patients: a pilot study. <i>PLoS One</i>, 6(1).</p>	Included	<p>Explores gender differences in plasma biomarker levels in patients with COPD and smokers without COPD.</p>
<p>Decramer, M., Molenberghs, G., Liu, D., Celli, B., Kesten, S., Lystig, T., . . . investigators, U. (2011, October). Premature discontinuation during the UPLIFT study. <i>Respiratory Medicine</i>, 105(10), 123-1530.</p>	Excluded	<p>No discussion of gender related to COPD. Focus on bronchodilator versus no bronchodilator</p>

Donaldson, G., Mullerova, H., Locantore, N., Hurst, J., Carlverley, P., Vestbo, J., . . . Wedzicha, J. (2013, July 30). Factors associated with change in exacerbation frequency in COPD. <i>Respiratory Research, 14</i> (1).	Excluded	No discussion of gender related to disease. No parameter clearly predicts an imminent change in exacerbation frequency category.
Ferrari, R., Tanni, S. E., Caram, L. M., Naves, C. R., & Godoy, I. (2011). Precitors of health status do not changer over three-year periods and exacerbation makes difference in chronic obstructive pulmonary disease. <i>Health & Quality of Life Outcomes, 9</i> (1).	Excluded	No gender-specific information. This is looking at disease progression as a whole, no comparison.
Ford, E. S., Mannino, D. M., Wheaton, A. G., Presley-Cantrell, L., Liu, Y., & al., e. (2014, April). Trends in the use, sociodemographic correlates, and unertreatment of prescription. <i>PLos One, 9</i> (4).	Included	The objective of this study was to examine trends in prescription medications for COPD among adults in the United States from 1999 to 2010. Utilizing this study for what management is used overall
Fuhrman, C., Roche, N., Vergnenegre, A., Zureik, M., Chouaid, C., & al., e. (2011, April). Hospital admissions related to acute exacerbations of chronic obstructive pulmonary disease. <i>Respiratory Medicine, 105</i> (4), 595-601.	Included	Hospitalization rates for AE-COPD have increased in France in recent years, especially among women. By contrast, AE-COPD-related in-hospital lethality has decreased.
Gerity, A. H., Thayer, L. M., Rinne, S., Liu, C. -F., Cook, M. A., & al., e. (2016). C14 finding the sweet spot between too much and too little care. <i>American Journal of Respiratory and Critical Care, 193</i> .	Excluded	Not related to gender differences. Focus is on NIV.
Grabicki, M., Kuznar-Kaminska, B., Rubinsztajn, R., Brajer-Luftmann, B., & Kasacka, M. (2019). COPD course and comorbidities: are there gender	Included	Clinical presentation, comorbidities and prognosis may differ between genders and may influence management decisions.

differences? <i>Advances in Experimental Medicine and Biology</i> , 43-51.		
Gupta, N., Pinto, L., Benedetti, A., Zhi, L. P., Tan, W. C., Aaron, S. D., . . . Bourbeau, J. (2016, November). The COPD Assessment Test: Can it discriminate across COPD subpopulations? <i>CHEST</i> , 150(5), 1069-1079.	Excluded	Primary population in study wasn't previously diagnosed with COPD.
Kesten, S., Celli, B., Decramer, M., Liu, D., & Tashkin, D. (2011, September). Adverse health consequences in COPD patients with rapid decline in FEV1 -- evidence from the UPLIFT trial. <i>Respiratory Research</i> , 12(9), 1-9.	Excluded	Doesn't look at genders. Focus is on FEV1 as predictor of disease status and progression.
Kim, J., Jae Yong Yoo, & Sun, K. (2019, May). Metabolic syndrome in south Korean patients with chronic obstructive pulmonary disease. <i>Asian Nursing Research</i> , 13(2), 137-146.	Excluded	Looking at correlation between COPD and metabolic syndrome, not gender differences of COPD management.
Kohler, M., Sandberg, A., Kjellqvist, S., Thomas, A., Karimi, R., & al., e. (2013, March). Gender differences in the bronchoalveolar lavage cell proteome of patients with chronic obstructive pulmonary disease. <i>Journal of Allergy and Clinical Immunology</i> , 131(3), 743-751.	Included	<u>Chronic obstructive pulmonary disease</u> (COPD) is a leading cause of morbidity and mortality worldwide and is increasing, primarily among women. In this study the soluble proteome of bronchoalveolar lavage cells, primarily consisting of macrophages, was investigated with the aim of identifying phenotypic differences in early disease development.
Kozu, R., Senjyu, H., Jenkins, S. C., Mukae, H., Sakamoto, N., & al., e. (2011). Differences in response to pulmonary rehabilitation in idiopathic	Excluded	No gender related discussion in this article.

pulmonary fibrosis and chronic obstructive pulmonary disease. <i>Respiration</i> , 81(3), 196-205.		
Liang, B. M., & Feng, Y. I. (2012 June). Association of gastroesophageal reflux disease symptoms with stable chronic obstructive pulmonary disease. <i>Lung</i> , 190(3), 277-282.	Excluded	Does not involve women specifically or gender comparison related to disease process.
Martinez, C., Rraparla, S., Plauschinat, C., Giardino, N. D., Rogers, B., Beresford, J., . . . Han, M. (2012). Gender differences in symptoms and care delivery for chronic obstructive pulmonary disease. <i>Journal of Women's Health</i> , 21(12), 1267-1274.	Included	Study utilized surveys to evaluate for gender differences relating to perceptions about symptoms, barriers to care, and sources of information about COPD.
May, C. R., Cummings, A., Myall, M., Harvey, J., Pope, C., & al., e. (2016). Experiences of long-term life-limiting conditions among patients and carers: what can we learn from a meta-review of systematic reviews of qualitative studies of chronic heart failure, chronic obstructive pulmonary disease and chronic kidney disease? <i>British Medical Journal</i> , 6(10).	Excluded	Multiple disease process, patient, and caregiver, not aligned with current subject
Miravittles, M., Iriberry, M., Barrueco, M., Lleonart, M., villarrubia, E., & Galera, J. (2013). Usefulness of the LCOPD, CAFS and CASIS scales in understanding the impact of COPD on patients. <i>Respiration</i> , 86(3), 190-200.	Excluded	Patients are not separated by gender in this.
Rabe, K., Fabbri, L., Vogelmeier, C., Kogler, H., Schmidt, H., Beeh, K., & Giaab, T. (2013, March). Seasonal distribution of COPD exacerbations in	Excluded	Patients are not separated by gender in this.

the prevention of exacerbations with tiotropium in COPD trial. <i>Chest</i> , 143(3), 711-719.		
Roberts, N., Patel, I., & Patridge, M. (2016, February). The diagnosis of COPD in primary care; gender differences and the role of spirometry. <i>Respiratory Medicine</i> , 111, 60-63.	Excluded	Study used to definitively diagnose COPD or refute.
Scioscia, G., Bianco, I., Arismendi, E., Burgos, F., Gistau, C., Foscino, B. M., . . . Augusti, A. (2017, February). Different dyspnoea perception in COPD patient with frequent and infrequent exacerbations. <i>Thorax</i> , 72(7), 117-121.	Excluded	Perception of dyspnea and its relationship to exacerbations. No gender specificity.
Spilling, C., Jones, P., Dodd, J., & Barrick, T. (2017). White matter lesions characterise brain involvement in moderate to severe chronic obstructive pulmonary disease, but cerebral atrophy does not. <i>BMC pulmonary Medicine</i> , 17, 1-12.	Excluded	Lacks any comparison between genders relating to subject of PICO
Torres, S. H., Montes de Oca, M., Loeb, E., Mata, A., & Hernandez, N. (2011). Gender and skeletal muscle characteristics in subject with chronic obstructive pulmonary disease. <i>Respiratory Medicine</i> , 105(1), 88-94.	Included	The present study was aimed to determine the differences in the skeletal muscle characteristics in men and women with and without COPD.
Vestbo, J., Agustí, A., Wouters, E., Bakke, P., Calverley, P., Celli, B., . . . Tal-Singer, R. (2014, May). Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team. <i>American</i>	Included	For progression of emphysema, the strongest predictors were continued smoking and female sex.

<i>Journal of Respiratory and Critical Care Medicine.</i>		
Wakabayashi , R., Motegi, T., & Kida, K. (2019, January). Gender differences in chronic obstructive pulmonary disease using the lung information needs questionnaire. <i>Sage Open Nursing, 5.</i>	Included	Proposal about why female women are more likely to develop COPD than men and other differences.
Wang, L., Tao, Y.-X., Dong, X.-Y., Zhang, Q., Zheng, H., Zheng, Y.-S., . . . Zhao, Y. (2017, February). Demographic, health behavioral, and self-management abilities associated with disease severity among patients with chronic obstructive pulmonary disease. <i>International Journal of Nursing Practice, 23</i> (1)	Included	The study highlighted the importance of physical activity, nutritional status, and gender difference in managing disease severity in COPD.
Wedzicha, J. A., Singh, D., Tsiligianni, I., Jenkins, C., Fucile, S., Fogel, R., . . . Kostikas, K. (2019, January 8). Treatment response to indacaterol/glycopyrronium versus salmeterol/fluticasone in exacerbating COPD patients by gender: a post-hoc analysis in the FLAME study. <i>Respiratory Research, 20</i> (1).	Included	Discussion of gender-specific response to treatment with these two medications.
Yormaz, B., Findik, D., & Suerdem, M. (2019, June). Differences of viral panel positive versus negative by real-time PCR in COPD. <i>the National Library of Medicine, 67</i> (2), 124-130.	Excluded	Looked at PCR in hospitalized patients during an exacerbation, didn't discuss gender in this study.

Table 4
Table of All Studies Included

Citation	Study Purpose	Pop (N) Sample Size (n) /setting(s)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Agusti, A., Peter, M., Celli, B., Coxson, H. O., Edwards, L. D., Lomas, D. A., . . . Vestbo, J. (2010). Characteristics of COPD heterogeneity in the ECLIPSE cohort. <i>Respiratory Research</i> , 122-135.	Describe the heterogeneity of COPD in a large and well characterized and controlled COPD cohort (ECLIPSE)	2164 COPD; 337 smokers with normal lung function; 245 never smokers	III	NA	Measured clinical parameters, nutritional status, spirometry, exercise tolerance, and amount of emphysema by computed tomography	The severity of airflow limitation in COPD patients was poorly related to the degree of breathlessness, health status, presence of comorbidity, exercise capacity and number of exacerbations reported in the year before the study. The distribution of these variables within each GOLD stage was wide. Even in subjects with severe airflow obstruction, a substantial proportion did not report symptoms, exacerbations or exercise limitation.	The clinical manifestations of COPD are highly variable, and the degree of airflow limitation does not capture the heterogeneity of the disease.
Bade, B. C., DeRycke, E. C., Ramsey, C., Skanderson, M., Crothers, K., & al., e. (2019, June). Sex differences in veterans admitted to the hospital for chronic obstructive pulmonary disease. <i>Annals of the American Thoracic Society</i> , 16(6), 707-714.	To determine risk factors for 30-day readmission among Veterans hospitalized for COPD	48,888 Veterans (4% women)	IV	Created and combined sex-stratified multivariate logistic regression models to identify associations	NA	Before hospitalization, women were less likely to have pulmonary function testing (76% vs. 78%; $P = 0.01$) or be treated with antimuscarinic (43% vs. 48%) or combined long-acting bronchodilator/inhaled	This study suggests differences between women and men hospitalized for COPD regarding presentation, evaluation, and management. Readmission is strongly influenced by comorbidities, suggesting individualized and comprehensive case management may reduce readmission risk for women and men with COPD.

	exacerbations and how they differed by sex.			with 30-day readmission.		corticosteroid (61% vs. 64%) inhalers. Women were more likely to receive nicotine-replacement therapy (all $P < 0.01$). Women had shorter length of stay (median days, 2 vs. 3; $P = 0.04$) and lower 30-day readmission rate (20% vs. 22%; $P = 0.01$). In adjusted models including both sexes, age, antimuscarinic use, comorbidities, and diagnosis of drug or alcohol use were associated with readmission; there was no association with sex and readmission risk.	
Breyer, M.-K., Rutten, E. P., Vernooij, J. H., Spruit, M. A., Dentener, M. A., & al., e. (2011, July). Gender differences in the adipose secretome system in chronic obstructive pulmonary disease (COPD): a pivotal role of leptin. <i>Respiratory Medicine</i> , 105(7), 1046-1053.	To investigate gender related differences in the adipokine metabolism in relation to systemic inflammatory biomarkers in clinically stable subjects	91 COPD; 35 Control (no COPD)	II	Lung function measurement for BMI with COPD subjects	NA	The COPD group was characterized by increased levels of CRP, IL-6, and Leptin. Plasma adiponectin and resistin concentrations were not different between the groups.	In men with clinically stable COPD, leptin adiponectin and resistin appear to be physiologically regulated while in women leptin metabolism is altered. Leptin secretion is increased in COPD women when compared to healthy women and compare to COPD men, and to a greater extent in overweight women with COPD.

	with COPD.						
Celli, B., Vestbo, J., Jenkins, C. R., Jones, P. W., Ferguson, G. T., & al., e. (2011, February 1). Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. <i>American Journal of Respiratory and Critical Care Medicine</i> , 183(3), 317-322.	Determine sex differences in survival, causes of death, and patient-centered outcomes in the 3-year Toward a Revolution in COPD Health (TORCH) study.	1,481 women and 4,631 men with COPD	III	NA	A trial comparing salmeterol, 50 µg, plus fluticasone propionate, 500 µg, twice a day and each component individually.	At baseline, women were younger (63 vs. 66 yr.), had higher FEV ₁ (47% vs. 44% predicted), and worse St. George's Respiratory Questionnaire (51.3 vs. 48.7) and Medical Research Council score. During the study, 707 (15.3%) men and 168 (11.3%) women died. After adjusting for differences in baseline factors, the risk of dying was 16% higher in men than in women; however, this was not statistically significant (hazard ratio 1.16 [95% CI, 0.98–1.39]). Causes of death were similar in women and men. Exacerbation rate was 25% higher in women than in men.	Women enrolled in TORCH had a lower mortality rate than men but similar causes of death. The risk of dying was similar in women and men after adjusting for important baseline variables. Women reported more exacerbations, and worse dyspnea and health status scores than men.
Criner, G. J., Martinez, F. J., Aaron, S., Agusti, A., Anzueto, A., & al., e. (2019, January). Current controversies in chronic obstructive disease. A report from the global initiative for chronic obstructive lung disease scientific committee. <i>Annals of the</i>	Review of current standards, informatics, and guidelines related to COPD	NA	I	NA	NA	Women do vary from men for COPD risk for development when exposed to or partaking in smoking. Women are more susceptible.	More research is needed to decipher best treatment options for women.

<i>American Thoracic Society, 16(1).</i>							
de Torres, J. P., Casanove, C., Pinto-Plata, V., Varo, N., P, R., & al., e. (2011). Gender differences in plasma biomarker levels in a cohort of COPD patients: a pilot study. <i>PLoS one, 6(1)</i> .	Explore gender differences in plasma biomarker levels in patients with COPD and smokers without COPD.	80 smokers without COPD (40 males, 40 females) and 152 stable COPD patients (76 males, 76 females) with similar airflow obstruction.	III	Measurement of plasma biomarkers	NA	The plasma biomarkers level explored were similar in men and women without COPD. In contrast, in patients with COPD the median value in pg/mL of IL-6 (6.26 vs 8.0, p=0.03), IL-16 (390 vs 321, p=0.009) and VEGF (50 vs 87, p=0.02) differed between women and men. Adjusted for smoking history, gender was independently associated with IL-16, PARC and VEGF levels. There were also gender differences in the associations between IL-6, IL-16 and VEGF and physiologic variables that predict outcomes.	In stable COPD patients with similar airflow obstruction, there are gender differences in plasma biomarker levels and in the association between biomarker levels and important clinical or physiological variables. Further studies should confirm our findings.
Ford, E. S., Mannino, D. M., Wheaton, A. G., Presley-Cantrell, L., Liu, Y., & al., e. (2014, April). Trends in the use, sociodemographic correlates, and unertreatment of prescription. <i>PLos One, 9(4)</i> .	Examine trends in prescription medication s for COPD among adults in the US from 1999-2010	1426	III	6 national surveys	N/A	Medications changed markedly from 1999-200 to 2009-2010. Many adults with COPD did not report having recommended prescription medications.	Increased need for additional research to discover barriers to patients filling and using prescription medications.

<p>Fuhrman, C., Roche, N., Vergnenegre, A., Zureik, M., Chouaid, C., & al., e. (2011, April). Hospital admissions related to acute exacerbations of chronic obstructive pulmonary disease. <i>Respiratory Medicine</i>, 105(4), 595-601.</p>	<p>We examined temporal trends in AE-COPD-related hospital admissions in France between 1998 and 2007.</p>	<p>Data were obtained from the French national hospital discharge database for patients aged at least 25 years. AE-COPD was identified with both a “narrow” and a “broad” definition, according to the position (primary or associated) of diagnoses, in order to ensure robustness.</p>	<p>III</p>	<p>Data were obtained from the French national hospital discharge database for patients aged at least 25 years. AE-COPD was identified with both a “narrow” and a “broad” definition, according to the position (primary or associated) of diagnoses, in order to ensure robustness.</p>	<p>NA</p>	<p>In 2007, among adults aged 25 years or more, the crude AE-COPD-related admission rates were 23/10000 in men and 10/10000 in women using the narrow definition. Using the broad definition, these rates were respectively 38 and 16/10000. With the narrow definition, the annual number of AE-COPD-related admissions increased by 38% between 1998 and 2007, while in-hospital <u>lethality</u> decreased from 7.6% to 6.0%. The proportion of male patients decreased from 72% to 68%. Similar trends were found using the broad definition. The age-standardized AE-COPD-related admission rate increased by 4.4% per year in women and by 1.6% per year in men with the narrow definition, and by respectively 3.8% and 1.2% with the broad definition. A strong seasonal pattern of admissions for AE-COPD was found, matching that of general practitioners</p>	<p>Hospitalization rates for AE-COPD have increased in France in recent years, especially among women. By contrast, AE-COPD-related in-hospital lethality has decreased.</p>
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						visits for <u>influenza-like illness</u> .	
Grabicki, M., Kuznar-Kaminska, B., Rubinsztajn, R., Brajer-Luftmann, B., & Kasacka, M. (2019). COPD course and comorbidities: are there gender differences? <i>Advances in Experimental Medicine and Biology</i> , 43-51.	The aim of this study was to evaluate significant differences between women and men suffering from COPD, regarding clinical presentation, pulmonary function test results, comorbidities, and prognosis.	470 patients with stable COPD with a history of smoking (152 women, 318 men, mean age 65.5 ± 8.8 vs. 66.6 ± 9.4 years, respectively)	III	Measurement of FEV1	NA	Women smoked less in comparison to men (30.4 vs. 41.9 pack-years, $p < 0.05$), showed more exacerbations (2.5 vs. 1.7, $p = 0.01$), higher forced expiratory volume in 1 s (FEV1%predicted), and increased residual volume/total lung capacity (RV/%TLC), but they had the same intensity of dyspnea. Women showed fewer comorbidities, on average, per patient (5.4 vs. 6.4, $p = 0.002$), but had a higher prevalence of at least seven comorbidities per patient (48.7% of women vs. 33.0% of men, $p < 0.05$). Women also had a significantly worse prognosis (4.6 vs. 3.1 BODE score, $p < 0.05$) that correlated with the number of comorbidities ($r = 0.33$, $p < 0.01$). In conclusion, this study strongly supports the existence of different gender phenotypes in COPD, especially	The gender difference may indicate a need for a targeted assessment and management of COPD in women and men.

						regarding exacerbations, comorbidities, and prognosis.	
Kohler, M., Sandberg, A., Kjellqvist, S., Thomas, A., Karimi, R., & al., e. (2013, March). Gender differences in the bronchoalveolar lavage cell proteome of patients with chronic obstructive pulmonary disease. <i>Journal of Allergy and Clinical Immunology</i> , 131(3), 743-751.	In this study the soluble <u>proteome of bronchoalveolar lavage</u> cells, primarily consisting of macrophages, was investigated with the aim of identifying phenotypic differences in early disease development.	NA	III	<u>Two-dimensional difference gel electrophoresis</u> was used for relative quantification of protein levels, and multivariate modeling was applied to identify proteins of interest that were subsequently identified by means of <u>liquid chromatography-mass spectrometry</u> .	NA	Significant gender differences were unveiled, with numerous alterations in the bronchoalveolar lavage cell proteome occurring in female but not male patients with COPD. Specifically, a subset of 19 proteins provided classification of female healthy smokers from female patients with COPD with 78% predictive power. Subsequent pathway analyses linked the observed alterations to downregulation of the lysosomal pathway and <u>upregulation</u> of the <u>oxidative phosphorylation</u> pathway, possibly linking dysregulation of macroautophagy to a female-dominated COPD disease phenotype.	This investigation makes an important contribution to the elucidation of putative molecular mechanisms underlying gender-based differences in the <u>pathophysiology</u> of COPD, linking alterations of specific molecular pathways to previously observed gender differences in clinical COPD phenotypes. Furthermore, these results stress the importance of the gender-specific search for biomarkers, diagnosis, and treatment in COPD.
Martinez, C., Raparla, S., Plauschinat, C., Giardino, N. D., Rogers, B., Beresford, J., . . . Han, M.	Mo Using data from a nationwide survey of	Data on 295 female and 273 male	III	Surveys were administered to a convenience	NA	Data on 295 female and 273 male participants were analyzed. With similar frequencies,	Significant gender-related differences in the perception of COPD healthcare delivery exist, revealing an opportunity to better understand what influences these

<p>(2012). Gender differences in symptoms and care delivery for chronic obstructive pulmonary disease. <i>Journal of Women's Health, 21</i>(12), 1267-1274.</p>	<p>patients with COPD, commissioned by a patient organization, the COPD Resource Network–National Emphysema/COPD Association (NECA), we evaluated potential gender differences in symptoms, barriers to care, and sources of information about the disease and the effect of socioeconomic and emotional factors on patient perceptions of care.</p>	<p>participants</p>		<p>sample of COPD patients to evaluate perceptions about symptoms, barriers to care, and sources of information about COPD.</p>	<p>women and men reported dyspnea and rated their health as poor/very poor. Although more women than men reported annual household income <\$30,000, no significant gender differences in frequency of health insurance, physician visits, or ever having had spirometry were detected. In adjusted models (1) women were more likely to report COPD diagnostic delay (odds ratio [OR] 1.66, 95% confidence interval [CI] 1.13-2.45, $p=0.01$), although anxiety (OR 1.83, 95% CI 1.10-3.06, $p=0.02$) and history of exacerbations (OR 1.60, 95% CI 1.08-2.37, $p=0.01$) were also significant predictors, (2) female gender was associated with difficulty reaching one's physician (OR 2.54, 95% CI 1.33-4.86, $p=0.004$), as was prior history of exacerbations (OR 2.25, 95% CI 1.21-4.20, $p=0.01$), and (3) female gender (OR 2.15, 95% CI 1.10-</p>	<p>attitudes and to improve care for both men and women.</p>
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						4.21, $p=0.02$) was the only significant predictor for finding time spent with their physician as insufficient.	
Torres, S. H., Montes de Oca, M., Loeb, E., Mata, A., & Hernandez, N. (2011). Gender and skeletal muscle characteristics in subject with chronic obstructive pulmonary disease. <i>Respiratory Medicine</i> , 105(1), 88-94.	a) to evaluate the gender differences of the skeletal muscle characteristics in COPD patients b) to explore the gender differences of the muscle characteristics in healthy subjects and c) to explore the differences by gender and COPD status in the skeletal muscle characteristics.	For comparison we studied 24 female (61 ± 9 years) and 30 male (65 ± 8 years) COPD patients with similar disease severity. In addition, healthy subjects, 17 women (58 ± 8 years), and 9 men (57 ± 8 years) were studied.	III	Pulmonary function, health status, six minute walk distance test (6MWD) and <u>vastus lateralis muscle</u> biopsy were assessed. Fiber type proportion, fiber type cross sectional area (CSA), capillary counts, and activity of <u>citrate synthase</u> (CS), <u>3-hydroxyacyl-CoA-dehydrogenase</u> (HAD) and <u>lactate-dehydrogenase</u> (LDH) were determined.	NA	Pulmonary function, health status and 6MWD were similar in male and female COPD patients. Fiber type distribution was similar between women (I = $42 \pm 9\%$, IIA = $39 \pm 13\%$, IIX = $19 \pm 7\%$) and men (I = $39 \pm 13\%$, IIA = $38 \pm 9\%$, IIX = $29 \pm 10\%$) with COPD, as well as CSA, capillarity and enzymes (CS 8.59 ± 1.6 vs. 9.74 ± 2.6 , HAD 9.03 ± 1.9 vs. 9.84 ± 2.5 , <u>LDH</u> 124 ± 48 vs. $151 \pm 68 \mu\text{mol min}^{-1} \text{g}^{-1}$). In normal subjects a decrease in type IIX fibers CSA was found in women compared with men (3703 ± 1478 vs. $5426 \pm 1386 \mu\text{m}^2$, respectively).	Female and male with COPD have similar skeletal muscle characteristics; it is possible that the disease blurs the gender differences. On the other hand, there seems to be fewer differences in muscle characteristics between older men and women, perhaps due to lower male <u>testosterone</u> levels and physical inactivity.

<p>Vestbo, J., Agusti, A., Wouters, E., Bakke, P., Calverley, P., Celli, B., . . . Tal-Singer, R. (2014, May). Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team. <i>American Journal of Respiratory and Critical Care Medicine</i>.</p>	<p>To characterize the heterogeneity and variability of COPD longitudinally.</p>	<p>2,164 patients with clinically stable COPD, 337 smokers with normal lung function, and 245 never-smokers</p>	<p>III</p>	<p>Measured a large number of clinical parameters, lung function, exercise tolerance, biomarkers, and amount of emphysema by computed tomography. All three groups were followed for 3 years.</p>	<p>NA</p>	<p>A striking heterogeneity among patients with COPD, with poor correlations between FEV1, symptoms, quality of life, functional outcomes, and biomarkers. Presence of systemic inflammation was found in only a limited proportion of patients, and did not relate to baseline characteristics or disease progression, but added prognostic value for predicting mortality. Exacerbations tracked over time and added to the concept of the "frequent exacerbator phenotype." Disease course was very variable, with close to a third of patients not progressing at all. Risk factors for 3-year change in both FEV1 and lung density were assessed. For FEV1 decline, continued smoking and presence of emphysema were the strongest predictors of progression; club cell protein was found to be a potential biomarker for disease activity. For progression of</p>	<p>By following a large, well characterized cohort of patients with COPD over 3 years, we have a clearer picture of a heterogeneous disease with clinically important subtypes ("phenotypes") and a variable and not inherently progressive course.</p>
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						emphysema, the strongest predictors were continued smoking and female sex.	
Wakabayashi , R., Motegi, T., & Kida, K. (2019, January). Gender differences in chronic obstructive pulmonary disease using the lung information needs questionnaire. <i>Sage Open Nursing</i> , 5.	To investigate gender-related information needs in patients with chronic obstructive pulmonary disease (COPD) using the Lung Information Needs Questionnaire (LINQ).	122	III	Cross sectional study. Patients with COPD receiving standardized self-management education including information regarding disease knowledge, medications, avoidance of exacerbation, smoking cessation, exercise, and nutrition were included. Gender differences were assessed by pulmonary function tests, 6-minute walking test, modified Medical	NA	Females displayed significantly higher information needs for total LINQ score ($p < .001$), avoidance of exacerbation ($p < .03$), and nutrition ($p < .006$). Significant correlations were seen between total LINQ score and gender ($p = .001$), forced expiratory volume in 1 second, % predicted ($p = .003$), and Mini-Mental State Examination ($p = .002$) for male patients. In females, modified Medical Research Council dyspnea scale was correlated with the total LINQ score ($p = .04$).	Behavioral differences in gender might have an effect on the long-term management of chronic diseases such as COPD.

				Research Council dyspnea scale, Mini-Mental State Examination, St. George's Respiratory Questionnaire, and LINQ.			
Wang, L., Tao, Y.-X., Dong, X.-Y., Zhang, Q., Zheng, H., Zheng, Y.-S., . . . Zhao, Y. (2017, February). Demographic, health behavioral, and self-management abilities associated with disease severity among patients with chronic obstructive pulmonary disease. <i>International Journal of Nursing Practice</i> , 23(1).	To identify the association between demographic characteristics, health behaviors, self-management abilities, and disease severity among patients with chronic obstructive pulmonary disease (COPD).	100	III	The DOSE index was assessed by grade of dyspnea (D), airflow obstruction (O), current smoking status (S), and frequency of exacerbation in the last year (E)	Self-management abilities were assessed by the COPD self-management scale. DOSE index associations with demographic characteristics, health behaviors, and self-management abilities were examined with multiple regression analysis.	In multiple regression analysis, physical activity, body mass index, and gender were negatively related to DOSE index.	The study highlighted the importance of physical activity, nutritional status, and gender difference in managing disease severity in COPD. Professional nurses should develop individualized intervention programs and specifically increase physical activity for men and poor nutritional status for patients with COPD.
Wedzicha, J. A., Singh, D., Tsiligianni, I., Jenkins, C., Fucile, S., Fogel, R., . . . Kostikas, K. (2019, January 8). Treatment response to indacaterol/glycopyrronium versus	Evaluate gender-based differences in the FLAME study	2557 men and 805 women	I	FLAME was a 52-week randomized controlled trial in patients with severe-to-	Bronchodilator, inhaled steroid combination	Baseline characteristics differed between genders, with women being younger, having better lung function and more often experiencing ≥ 2	Although there were gender differences in baseline characteristics, IND/GLY demonstrated similar trends for exacerbation prevention and lung function improvement in men and women with moderate-to-very-severe COPD and a history of exacerbations compared with

<p>salmeterol/fluticasone in exacerbating COPD patients by gender: a post-hoc analysis in the FLAME study. <i>Respiratory Research</i>, 20(1).</p>	<p>population in terms of baseline characteristics and efficacy outcomes.</p>			<p>very-severe COPD and a history of exacerbations . In this post-hoc analysis, gender-based baseline differences and treatment outcomes between indacaterol/glycopyrronium 110/50 µg once daily (IND/GLY) and salmeterol/fluticasone 50/500 twice daily (SFC) were assessed in terms of rate of exacerbations , time-to-first exacerbation, lung function, health status, and rescue medication use.</p>	<p>exacerbations in the previous year. Compared with SFC, IND/GLY treatment was associated with reductions in the annualized rates of moderate/severe exacerbations (rate ratio [95% CI]: 0.81 [0.73-0.91], 0.89 [0.74-1.07] in men and women, respectively). Similarly, time-to-first moderate/severe exacerbation was also delayed (hazard ratio [95% CI]: 0.79 [0.70-0.89] and 0.76 [0.63-0.91] in men and women, respectively). Results were similar for all (mild/moderate/severe) exacerbations. Improvements in lung function, health status and rescue medication use with IND/GLY vs SFC were comparable between men and women. The smaller sample size for women may account for some observed discrepancies in treatment responses.</p>	<p>SFC. Small differences in the effects seen between genders may be attributed to the different sizes of the two groups and need to be further evaluated in randomized trials that are appropriately powered for gender analysis.</p>
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