

**An investigation into the use of selective serotonin reuptake inhibitors for improving  
low lung function and pulmonary exacerbations**

Hilary F. Armstrong

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## **Abstract**

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Chronic obstructive pulmonary disease (COPD) is characterized by periodic episodes of worsening symptom (e.g., shortness of breath, irregular breathing, and worse coughing with increased phlegm production), also called pulmonary exacerbations. Inflammation is an important cause of reduced lung function as inflammation contributes to airflow obstruction in the small airways and lung parenchyma [1]. Even in individuals with mild COPD [2], inflammation reduces lung function, accelerates decline in lung function overtime, and increases the risk for respiratory exacerbations [3-7]. Agents that reduce systemic inflammation are hypothesized to decrease the inflammation in the lungs, resulting in improvements in lung function and a decrease in exacerbation frequency. We hypothesize that antidepressants have a beneficial effect on lung function. In addition to having anti-inflammatory properties, antidepressants act upon serotonin, which is integral in central breathing control. The combination of the anti-inflammatory and serotonergic effects may provide users of selective serotonin reuptake inhibitors with a lung function benefit while avoiding the side effects of steroids. This dissertation assesses whether selective serotonin reuptake inhibitors increase concurrent lung function and reduce the risk for respiratory exacerbations. It consists of three parts: a systematic literature review and two analytic papers using large prospective databases. The systematic review of the literature identified limitations concerning the effect of selective serotonin reuptake inhibitors on lung function. Overall, the analytic papers found no support for a beneficial association between selective serotonin reuptake inhibitors and spirometry, dyspnea or pulmonary exacerbations; indeed the association was in the opposite direction as hypothesized. In addition, there was no support for meaningful mediation by inflammatory markers. Further research is needed to determine if selective serotonin reuptake inhibitors have a harmful effect on lung function and pulmonary exacerbations.

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## CHAPTER 1. INTRODUCTION

COPD refers to a group of diseases that cause airflow obstruction, respiratory muscle weakness, and breathing-related problems (such as increased breathlessness, frequent coughing, and tightness in the chest) that result in reduced lung function [8]. Symptoms include shortness of breath (or dyspnea), persistent (chronic) cough, wheezing and labored breathing during physical activity. Recent estimates suggest there are approximately 12-16 million men and women with COPD in the U.S. and 52 million worldwide [9]. However, the actual prevalence of low lung function is likely under-estimated since potentially treatable mild cases of obstructive lung disease often go undetected [10]. Respiratory exacerbations, a sudden worsening of respiratory symptoms and airway function, are also a concern for COPD patients and their practitioners. Currently, there is no cure for COPD; therefore, practitioners focus on reducing the risk of respiratory exacerbations and mortality and improving symptoms as the primary treatment goals [11].

Inflammation plays a large role in COPD, as evidenced by the Global Initiative for Chronic Obstructive Lung Disease classifying COPD as an inflammatory disease [8]. As the pathogenesis of COPD becomes better understood, systemic inflammation is hypothesized to be responsible for many symptoms leading to a reduction in quality of life [12, 13]. Current treatments for COPD are therefore targeted at reducing inflammation [14, 15]; however, no medication indicated for COPD treatment has satisfactorily done so [14, 15] and most result in significant adverse outcomes.

Adverse events and a lack of efficacy leads researchers to consider other drugs. Some antidepressants, namely selective serotonin reuptake inhibitors, may have off-label uses in treating COPD symptoms. Selective serotonin reuptake inhibitors are anti-inflammatory and act upon serotonin, which is integral to central breathing control [16, 17]; this combination may provide an additional benefit over current COPD treatment regimes.

While there is evidence for the underlying biological mechanism, very few studies have actually tested the effect of antidepressants on lung function. This dissertation aims to test whether participants on selective serotonin reuptake inhibitors have better concurrent lung function and a lower risk for respiratory exacerbations than those not on selective serotonin reuptake inhibitors.

The dissertation consists of three parts: a systematic literature review and two analytic research papers investigating the effect of selective serotonin reuptake inhibitors on lung function and respiratory exacerbations. First, the systematic literature review critically evaluates the existing literature and identifies what further evidence would be required to warrant the use of selective serotonin reuptake inhibitors for lung function improvement. Two analytic chapters follow the systematic review. These are written to determine whether selective serotonin reuptake inhibitors increase concurrent lung function and lower the risk for exacerbations. Using a large population-based dataset, the Multi Ethnic Study of Atherosclerosis, Chapter 3 assesses whether those on selective serotonin reuptake inhibitors have better lung function than those not on selective serotonin reuptake inhibitors and if those who switch their medication status have a greater change in lung function than those who remained consistently on or off selective serotonin reuptake inhibitors. In Chapter 4, we use the Subpopulations and Intermediate Outcome Measures in COPD Study to investigate whether those on selective serotonin reuptake inhibitors have a lower risk for respiratory exacerbations than those not on an antidepressant or on other antidepressants, and whether the association between selective serotonin reuptake inhibitors and lung function is partly mediated by inflammatory markers. Lastly, an integration and discussion of the findings is provided in Chapter 5. This dissertation aims to provide information on whether selective serotonin reuptake inhibitors can be used to improve reduced lung function and see if further investigation is warranted in the form of interventional prospective studies.

## CHAPTER 2. THE ASSOCIATION OF ANTIDEPRESSANTS AND LUNG FUNCTION: A SYSTEMATIC REVIEW

### ABSTRACT

*Background:* Chronic lower respiratory diseases, which include chronic obstructive pulmonary disease, asthma, emphysema and chronic bronchitis, are now the third leading cause of death in the US and the fourth leading worldwide. Current treatments for chronic obstructive pulmonary disease aim at reducing inflammation; however, there is room for improvement as no medications influence central breathing control in COPD. Some antidepressants are anti-inflammatory and act upon the neurotransmitter serotonin, which is integral to central breathing control; this combination may provide an additional benefit over current chronic obstructive pulmonary disease treatment regimes. *Objectives:* This paper aims to systematically review the empirical research on the relationship between antidepressants and lung function. Furthermore, this paper assesses whether the variation in observed associations can be explained by antidepressant type. *Data sources:* MEDLINE, PsychINFO, EMBASE and COCHRANE were searched from inception of the search engine until June 1, 2016. The search strategy used medical subject headings (MeSH) and text word terms relating to lung function and antidepressants. *Study selection:* Peer reviewed research reports on humans, written in English, including a clinically relevant lung function measurement as an outcome, and assessing the effect of at least one antidepressant were evaluated for eligibility. *Data collection and analysis:* In addition to lung function outcomes, data extraction included first author, year of publication, study design, information regarding participant characteristics, type and dose of antidepressant, attrition, and duration of intervention. For studies that had more than one measure of lung function, we recorded results for each measure. *Main results:* Twenty-three publications were included in the review, reporting 24 separate studies. The 24 studies covered four types of antidepressants: selective serotonin reuptake inhibitors, tricyclic antidepressants, and other antidepressants (type not always given). Many of the studies reported both dyspnea and spirometry and used multiple measures of assessment. Overall, there were 21 studies with spirometry as an outcome. For selective serotonin reuptake inhibitors, 40% of the studies had a significant association and 42% of tricyclic antidepressant studies had a significant association with improvement in spirometry. Eleven studies assessed dyspnea as an outcome. For selective serotonin

reuptake inhibitors, 33% of the studies had a significant association; for tricyclic antidepressants, 25% of the studies had a significant association with improvement in dyspnea. *Conclusions:* Results tended to vary by inclusion of participants with comorbid depression, severity of lung function impairment, and type of antidepressant. The information provided in these studies suggest the potential for certain antidepressants to improve lung function but requires further investigation using population-based data.

## INTRODUCTION

Chronic lower respiratory diseases, primarily chronic obstructive pulmonary disease (COPD), is now the third leading cause of death in the United States [18] and the fourth leading worldwide [19]. Recent estimates suggest there are approximately 12-16 million men and women with COPD in the U.S. and 52 million worldwide [9]. However, the actual prevalence of low lung function is likely under-estimated since potentially treatable mild cases of obstructive lung disease often go undetected [10]. A study from the National Health and Nutrition Examination Survey demonstrated that many US adults have low lung function but no reported lung disease diagnosis [10]. Even in those who are asymptomatic, low lung function can have debilitating effects. For example, the leading cause of death from COPD is respiratory failure, however the majority of those with mild-to-moderate COPD die from cardiovascular disease which likely occurs from chronic low-grade inflammation, a common cause of both COPD and cardiovascular disease [20].

### *The need for more effective medication*

As the pathogenesis of COPD becomes better understood, inflammation is hypothesized to be responsible for many symptoms leading to a reduction in quality of life [12, 13]. Current treatments for COPD are therefore targeted at reducing inflammation [14, 15]. For example, inhaler-based steroids for long-term treatment of COPD are used for symptom control and prevention of pulmonary exacerbations [12]. Due to their anti-inflammatory effects, inhaled corticosteroids can improve short-term pulmonary function and dyspnea, shorten hospitalizations, and decrease the frequency of exacerbations [21, 22]. Most studies however have found that regular treatment with inhaled corticosteroids alone does not change the long-term decline of FEV1 nor mortality in participants with COPD [23, 24]. Inhaled corticosteroid use is also associated with a higher prevalence of oral candidiasis, hoarse voice, skin bruising, and pneumonia [24]. Results from observational studies also suggest that inhaled corticosteroids are associated with increased risk of diabetes [25], cataracts [26], and mycobacterial infection [27]. Adverse events and a lack of efficacy leads researchers to consider other drugs. For

example, observational studies have shown statins, approved as lipid-lowering agents, are useful in COPD due to their anti-inflammatory effects [14, 28-30].

Like statins, some antidepressants, particularly selective serotonin reuptake inhibitors, may have off-label uses in treating COPD symptoms. Selective serotonin reuptake inhibitors are anti-inflammatory and act upon serotonin, which is integral to central breathing control [16, 17]; this combination may provide them with an additional benefit over current COPD treatment regimes.

### *Antidepressants*

Major types of antidepressants include tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Generally, the choice of an antidepressant depends on finding a medication that works with an individual's needs and tolerance of side effects. Selective serotonin reuptake inhibitors have the lowest side effect profile compared with older antidepressants and are the most widely prescribed [31]. Possible side effects of selective serotonin reuptake inhibitors are generally mild but include drowsiness, nausea, dry mouth, some sexual side effects, insomnia and dizziness [31]. In general, these side effects are milder, or similar, to the side effects of current COPD drugs.

### *Effect of selective serotonin reuptake inhibitors on inflammation*

Seen in both animal [32-34], and human [16] models, selective serotonin reuptake inhibitors reduce the microglial production of the pro-inflammatory-cytokine tumor necrosis- $\alpha$  and the free radical nitric oxide, both key players in inflammation in the brain [35]. In an animal model of the lungs, fluoxetine, a selective serotonin reuptake inhibitor, inhibits airway inflammation through affecting the capacity of monocytes and lung epithelial cells to produce inflammatory cytokines [36]. These effects are potentially due to selective serotonin reuptake inhibitors' influence on serotonin, as serotonin has a role in anti-inflammatory processes [33, 37].

Although tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors are all thought to have serotonergic effects, in two similar studies by Bianchi,

only selective serotonin reuptake inhibitors increase the level of serotonin, resulting in anti-inflammatory effects [33, 37]. Additional trials show that serotonin-norepinephrine reuptake inhibitors [16] and tricyclic antidepressants [38] do not have anti-inflammatory effects.

The narrowly targeted action of selective serotonin reuptake inhibitors on serotonin may explain the discrepancy between the effects of selective serotonin reuptake inhibitors and other classes of antidepressants on inflammation. Selective serotonin reuptake inhibitors do not increase norepinephrine, but both tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors do [39]. Consistent with the known pro-inflammatory effects of norepinephrine on innate immune cells [40], serotonin-norepinephrine reuptake inhibitors are associated with an *increase* in inflammatory markers [41], suggesting that norepinephrine may cancel out the anti-inflammatory effects of serotonin.

#### *Serotonin, breathing control, and dyspnea*

In addition to anti-inflammatory pathways, serotonin is involved in the central control of breathing [17]. The serotonin transporter, a protein that transports serotonin and regulates plasma serotonin levels [42], is highly expressed in the lungs, predominately in pulmonary-artery smooth muscle cells. The serotonin transporter is important in maintaining patent upper airways [43] and affects phrenic nerve activity [44]. Since the serotonergic system is linked to respiratory function, serotonergic drugs may increase the coordination and force-generating capacity of the weakened respiratory muscles seen in COPD [45], resulting in decreased upper-airway resistance. Additionally, serotonin modulates the central control of breathing in part by decreasing sensitivity to carbon dioxide [46]. In participants with COPD, greater degrees of carbon dioxide sensitivity are associated with more severe dyspnea [47]. In light of this link with carbon dioxide, researchers have suggested that drugs that increase serotonin levels may also have anti-dyspneic effects [48].

Due to the evidence presented above, we hypothesize that selective serotonin reuptake inhibitors may improve lung function through the combination of their anti-inflammatory and serotonergic effects.

## **PURPOSE**

Previous studies provide evidence for an association between lung function and antidepressants; however, to our knowledge a systematic review of the literature has not been performed. The purpose of this paper is to systematically review the empirical research on the relationship between antidepressants and lung function in humans. Furthermore, this paper assesses whether variation in observed associations can be explained by antidepressant type.

The study goal is as follows:

1. To critically evaluate the existing literature and identify what further evidence would be required to warrant the use of antidepressants for lung function improvement.

## **METHODS**

### *Information sources and search criteria*

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [49]. We searched MEDLINE, PsychINFO, EMBASE, and COCHRANE from inception of the search engine until June 1, 2016. The search strategy uses medical subject headings (MeSH) and text word terms. For lung function, the terms include “respiratory function tests”, “spirometry”, “pulmonary ventilation”, “forced expiratory volume”, “dyspnea”, “breath shortness”, “shortness of breath”, “breathlessness”, “breathing discomfort”, and “respiratory symptoms”. The antidepressant terms include “antidepressive agents”, “serotonin uptake inhibitors”, “monoamine oxidase inhibitors”, “tricyclic antidepressive agents”, as well as individual antidepressants (e.g. citalopram, sertraline, and amitriptyline). We searched using the combination of lung function and antidepressant terms (requiring at least one of each). Additional studies were found through the reference lists of the articles selected for review.

### *Eligibility criteria*

The inclusion criteria are: 1- peer-reviewed research report (case studies were excluded); 2- written in English; 3- includes spirometry or dyspnea as an outcome (see measures section below); 4- assesses the effect of at least one antidepressant; 5- study of humans.

Two outcome measures of lung function were assessed: spirometry and dyspnea.

Spirometry: Spirometry assesses how well the lungs work by measuring how much air is inhaled, how much is exhaled, and how quickly you exhale. Spirometry is often used in diagnosing pulmonary disease since it is standardized and the current gold standard for objectively defining airflow obstruction [50]. A decreased forced expiratory volume in one second (FEV<sub>1</sub>), the maximal volume of air expired in the first second after a full inspiration [50], is the measure primarily used to show reduced lung function in COPD [51]. Predicted reference values have been calculated and compared with samples of healthy subjects drawn from the general population to yield percent predicted (%) standards.

Dyspnea: Dyspnea is the main symptom perceived in participants affected by chronic respiratory diseases [52]. Even modest improvements in dyspnea are likely to determine clinically relevant changes in patient quality of life. There are numerous modes for classifying and characterizing the tools used to assess dyspnea, which are all self-reported. Types of scales include “discriminative” (that differentiate study populations based on the level of perceived dyspnea), “evaluative” (that identify variations with respect to a baseline condition), and “categorical” (which quantify the symptom according to categories). While these scales are associated with parameters of physiological impairments, they are not well interrelated [53, 54].

#### *Study selection*

We examined the titles and abstracts to remove reports not meeting eligibility criteria. If it was not clear from the title or abstract that the study should be excluded, the full text was assessed. The same approach was used for additional publications identified through the reference lists of relevant papers.

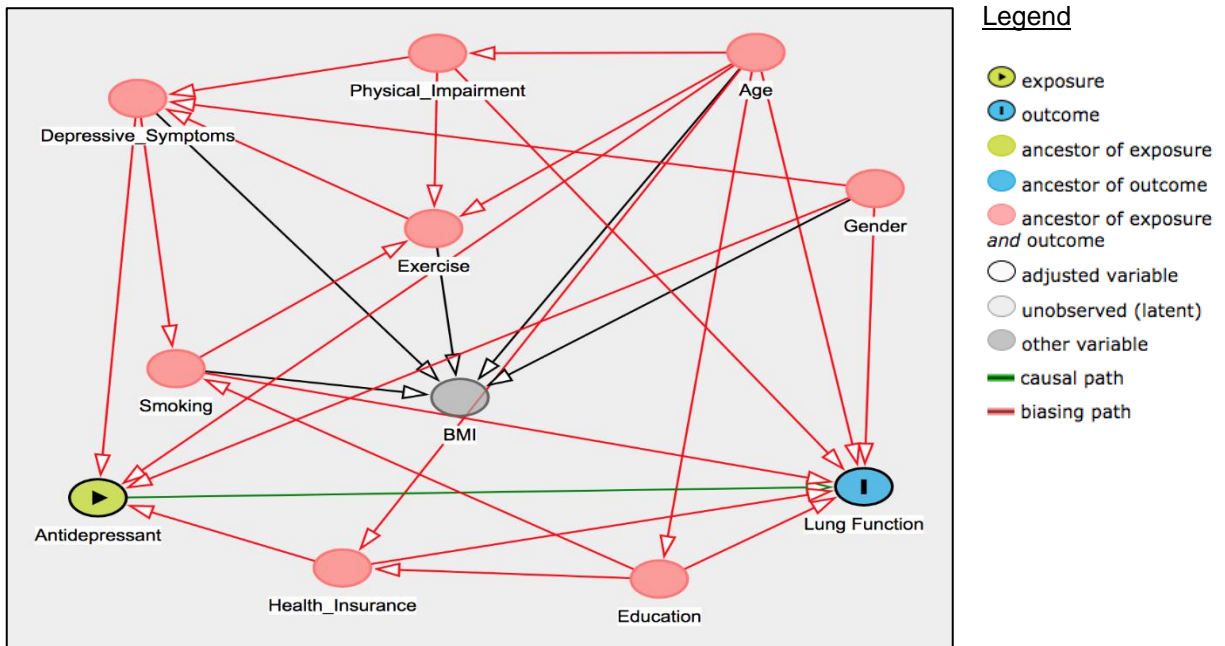
#### *Data extraction*

In addition to lung function outcomes, data extraction included first author, year of publication, study design, information regarding participant characteristics, type and dose of antidepressant, attrition, and duration of intervention (if applicable). For studies that had more than one outcome (spirometry and dyspnea), we recorded results for each. Study design was inferred from the study description used by the

authors. If the study design was not stated, it was marked as unknown; however, we were usually able to infer what it was and noted the potential design. The same procedures apply to the sample recruitment. Results are reported as mean±SD, except where noted.

*Study quality*

We assessed all studies for methodological quality for the following conditions: study participation, study attrition, outcome measurement and reporting, and study confounding. Criteria for each domain are listed in **Appendix Figure 1**. Directed Acyclic Graph for hypothesized confounders with lung function in the MESA study



Appendix Figure 2. Directed Acyclic Graph for hypothesized confounders with exacerbations in the SPIROMICS study

Legend

Appendix Table 1 *Error! Reference source not found.* and were modified from a previous study [55]. A judgement and support for each entry are given in the 'Risk of bias' table; the judgement for each entry assesses the risk of bias as 'low risk' or 'high risk'; if there was not enough information given in the study to determine adequacy, it was marked as 'unclear'.

### *Investigation of heterogeneity*

We explore possible clinical or methodological reasons for variation by subgrouping studies based on characteristics that are potentially responsible for differences in outcomes. We considered if the following are likely to explain differences between and within studies: study design, population, intervention and setting, or the type of outcome measure(s) used. We categorized the effects into three categories: effects that were statistically significant ( $p < 0.05$ ) and in the hypothesized direction (i.e. supported the hypothesis), non-significant effects regardless of direction, and significant effects in the opposite direction (i.e. evidence against the hypothesis).

This review begins with a synthesis of the findings of the included studies. We then stratify the results by antidepressant type and outcome assessed (spirometry or dyspnea) to identify patterns across the included studies, followed by an assessment of the study quality, and conclude with a discussion of the potential effect moderators.

## **RESULTS**

### *Article selection*

**Figure 2.1** provides the process of article selection for inclusion in the present systematic review. Electronic database searches yielded 3,485 unique results. We then examined the titles and abstracts of publications identified for eligibility. After this screening, we reviewed the remaining reports to determine agreement with inclusion criteria and examined references from the selected papers to look for other references not yet included; this resulted in a set of 67 articles. Of these manuscripts, 44 were considered ineligible including 10 that did not include a lung function measurement as an outcome, 24 that were case studies, abstracts or reviews, 2 that did not test the effect of at least one potential antidepressant, 4 that

were published in languages other than English, 2 that were animal studies, and 2 that were duplicates of the exact same trials. This yielded 23 articles for review.

### *Study characteristics*

While 23 publications are included in the review, one paper [56] reported two studies within the same publication; therefore, 24 separate studies are considered and reported below. A summary of the study characteristics stratified by antidepressant type is provided in **Table 2.1**.

The 24 studies covered four types of antidepressants; 8 of the studies assessed selective serotonin reuptake inhibitors (Column A) [45, 56-61], 12 evaluated tricyclic antidepressants (Column B) [62-73], and the other four studies used tianeptine [74], mianserin [75], or multiple antidepressants (type not always given) [76, 77]- grouped together as 'other antidepressants' (Column C). Tianeptine *increases* serotonin uptake in the brain (in contrast with most antidepressant agents) while mianserin is a tetracyclic antidepressant, closely related to tricyclic antidepressants.

The largest proportion of studies used a crossover design (33%), closely followed by cohort (29%), and then randomized controlled trials (RCTs) (21%). There was one case control study by Adams et al. who performed a long-term follow up of a previous randomized, double-blind, placebo-controlled trial [70]. The only large cohort study was by van Milligen et al. who analyzed cross sectional data to assess the association between depression and physical function [77]. The sample size ranged from six to 2,258 with the approximately half (46%) of the studies having between one and 20 participants. Almost 80% of the studies recruited participants from the outpatient population. The study duration ranged from one day [71] to long-term follow-ups lasting one to three years [70]. While the majority of studies assessed participants with COPD (58%), others included asthma, cystic fibrosis, and those without any respiratory disorders. This variation in disease states lead to a wide range in study-specific baseline FEV1 (0.62 to 3.58 liters and 22.3 to 107.1 percent predicted). A quarter of the studies did not present any information on the baseline FEV1 of the participants. Of those that did, 12 presented it in liters only and nine in percent predicted only; three reported both liters and percent predicted [56, 63, 76]. Half of the studies included between 26-50% of females, with a range from zero to 80.5%. All but one study [74] enrolled adult participants, with an average

age of  $49.8 \pm 7.2$  years. However, even excluding the study of children, the mean age still varied widely (28.4 to 70.5 years). Both participants with and without comorbid depression were eligible for inclusion in this review. Approximately half of the studies included participants with comorbid depression (54%).

### *Study results*

Many of the 24 studies report both dyspnea and spirometry and used multiple measures for assessing each measure; 21 studies measured spirometry and 11 measured dyspnea. While spirometry is standardized in how it is measured, 12 studies presented FEV1 in liters and nine in percent predicted, making the results non-comparable. The dyspnea measurements ranged widely with nine distinct scales being used across 11 studies (**Appendix Table 2**). Of the 11 studies that included dyspnea measurements, only one used a diary to keep track of patient's dyspnea outside of the hospital. Because of the various disease states, study designs, and statistical techniques used, we noted substantial clinical, methodological, and statistical heterogeneity across included studies and therefore were unable to report pooled results from a meta-analysis and instead use a narrative approach to data synthesis.

To assess the general results when the authors use different metrics, we categorized studies into 'significant', when they were in the hypothesized direction and statistically significant, 'non-significant' when they were non-significant regardless of the direction of effect; and 'unexpected' if they were in the opposite direction as hypothesized. We found that 38% were significant, 58% non-significant and 4% unexpected.

### *Results across antidepressant types*

We stratified the results by antidepressant type since we hypothesized that there is a difference in the magnitude of association between antidepressant types. We will first present the spirometry results by antidepressant type, then the dyspnea results. Detailed results for individual studies are presented in **Appendix Table 3**.

### Spirometry

### *Selective serotonin reuptake inhibitors (Table 2.2, Column A)*

Five of the studies using selective serotonin reuptake inhibitors assessed spirometry as an outcome [45, 58, 59, 78]. Two (40%) of these showed a significant association between selective serotonin reuptake inhibitors and increased lung function. Momtaz et al. studied two groups of age and sex matched severe COPD participants (n=50), one of which received fluoxetine [59]. After 3 months on the antidepressant, the treatment group increased their FEV1 from  $1.10\pm 0.49$  to  $1.20\pm 0.44$  liters ( $p=0.01$ ); the group that did not receive antidepressant had no change in FEV1. In the study by Perna et al., six participants were treated with citalopram, after 1-month their FEV1 significantly increased ( $p<0.05$ ) from  $0.91\pm 0.17$  to  $1.12\pm 0.15$  liters [45].

In contrast, the study by Papp et al. (statistics not reported) [58] and two studies by Eiser et al. (change in FEV1 for the treatment group:  $1.14\pm 0.65$  (baseline) to  $1.18\pm 0.70$  liters (post 3 months) (open-label cohort study),  $p=0.22$  and  $1.13\pm 0.64$  (baseline) to  $1.12\pm 0.69$  liters (post 6 weeks),  $p=0.43$  (double-blind cohort study)) found no significant association between selective serotonin reuptake inhibitors and spirometry [78].

In summary, there were two studies using selective serotonin reuptake inhibitors with significant associations that assessed spirometry (one cohort, one pre/post comparison, average sample size=28) and three non-significant studies (two cohort and one crossover, average sample size=25). Overall, regardless of significance, the four studies that reported quantitative spirometric outcomes had an average difference in FEV1 (in liters) of 0.09 (range: -0.01 to 0.21) between those on and off selective serotonin reuptake inhibitors. There were no selective serotonin reuptake inhibitor studies that reported FEV1 as percent predicted.

### *Tricyclic antidepressants (Table 2.2, Column B)*

All twelve studies involving tricyclic antidepressants included spirometry as an outcome [62-70, 72, 73, 79], five (42%) of these showed a significant association between tricyclic antidepressants and spirometric measures [69, 70, 72, 73, 79].

In the pre/post comparison study by Sugihara et al., 60 hospitalized patients and outpatients with bronchial asthma were given amitriptyline [69]. There were only descriptive results reported in this study, labeling the responses to therapy as 'excellent', 'good', or 'poor'. While the authors explained the definitions for each category, (i.e. a grade of 'excellent' meant subjective and objective symptoms had disappeared completely) no quantitative results were reported and they did not discriminate between spirometry and dyspnea. Meares et al. performed a study with an intramuscular injection of amitriptyline in 12 asthmatics, they reported significant improvements in 11 out of 12 participants (mean FEV1 improved from 2.02 to 2.37 liters) [79]. Riethmuller et al.'s study consisted of 36 cystic fibrosis participants enrolled in a randomized, double-blind, placebo-controlled crossover study of amitriptyline [73]. After 14 days of treatment, FEV1 improved significantly in the 25 mg amitriptyline group relative to placebo (absolute change in FEV1 percent predicted of  $+3.0 \pm 4$  and a relative change of  $+4.0 \pm 7.0$ ,  $p=0.048$ ). Of note, the researchers did not observe a significant change in lung function when participants took 50 mg or 75 mg of amitriptyline, showing there was not a dose response. In the same group that published the study by Riethmuller, Nahrlich et al.'s study assessed both the per-protocol (PP) and intent-to-treat (ITT) groups in a similar study of cystic fibrosis patients and found both to have significant increases in FEV1 (PP: treatment group  $+2.2 \pm 5.2$  change in FEV1 percent predicted from baseline, placebo  $-2.7 \pm 5.0$  change in FEV1 percent predicted from baseline,  $p=0.013$ ; ITT: treatment group  $+0.6 \pm 5.7$  change in FEV1 percent predicted from baseline, placebo  $-3.8 \pm 6.9$  change in FEV1 percent predicted from baseline,  $p=0.034$ ) [72]. After the studies by Riethmuller et al. and Nahrlich et al. were completed, some of the cystic fibrosis participants continued to take amitriptyline; Adams et al. followed twenty participants on amitriptyline for one, two, and three years compared with 14 control participants [70]. The lung function of cystic fibrosis participants, measured as FEV1 percent predicted, improved significantly in the treatment group each year (average of ~5%). In contrast, the control group's FEV1 percent predicted consistently decreased by 1 to 2.6%.

Two studies, both published by Series et al., reported no significant change in FEV1 (baseline:  $40.8 \pm 3.9\%$ , week 10:  $46.0 \pm 3.9\%$  [66]; baseline:  $1.04 \pm 0.12$  liters, week 10:  $1.21 \pm 0.10$  liters [67]). Gordon et al reported that FEV1 tended to be higher after treatment with desipramine ( $770 \pm 262$  mL) compared with placebo ( $657 \pm 225$  mL), but this did not reach statistical significance [64]. In the study by Carroll et al., the

authors reported no differences between groups for spirometry, however no numbers are reported for FEV1 even though it was stated as being measured [63]. In the study by Light et al., there were no substantial differences between the treatment ( $0.80\pm 0.21$  liters) and placebo ( $0.82\pm 0.25$  liters) groups [65]. Similarly, in the study by Strom et al., there were no differences between the treatment ( $0.7\pm 0.3$  liters) and control ( $0.7\pm 0.3$  liters) groups [68]. The study by Borson et al. reported that there were no differences between the treatment and control groups, although pulmonary numbers were not reported [62].

In summary, there were five studies using tricyclic antidepressants with significant associations that assessed spirometry (two pre/post comparison studies, one crossover, one RCT and one case control / long-term follow-up of a previous study; average sample size=34) and seven non-significant studies (two cohort, four crossover, one RCT; average sample size=16). Regardless of significance, for the five studies that reported quantitative spirometric outcomes, the average difference of FEV1 (in liters) was 0.11 (range: -0.005 to 0.35) between those on and off tricyclic antidepressants. Four studies used FEV1 percent predicted and the average difference reported was 4.4% (range: 2.2 to 7.2%).

#### *Other antidepressants (Table 2.2, Column C)*

There were four studies using antidepressants that were not selective serotonin reuptake inhibitors or tricyclic antidepressants; therefore, we combined them into a category of 'other antidepressants'. Two (50%) of these studies had significant associations with improved FEV1. Nascimento enrolled panic disorder participants and had them washout from their regular drug regime and re-tested after 1 week [76]. The majority (64%) were on imipramine + clonazepam, the rest were on clonazepam alone, paroxetine + clonazepam, paroxetine alone, or imipramine alone; FEV1 was significantly higher when on anti-panic drugs ( $3.58\pm 0.71$  liters,  $107.09\pm 13.74\%$ ) than after the washout period ( $3.42\pm 0.67$  liters,  $101.81\pm 14.40\%$ ). Lechin et al. assessed tianeptine in children with asthma for 52 weeks; they reported that tianeptine, but not placebo, provoked a dramatic increase in FEV1 [74]. The RCT study by Grove et al. reported no effect of mianserin (baseline: 0.92 liters, placebo: 0.90 liters, mianserin: 0.82 liters) [75].

Only one study found a significant association in the unexpected direction. Van Milligen et al. performed a large cohort analysis in persons with current depressive and/or anxiety disorders ( $n=1629$ ) and healthy controls without a lifetime diagnosis of these disorders ( $n=629$ ) [77]. The authors reported that

women using antidepressants have significantly poorer lung function compared with those with pure anxiety disorder (adjusted for age, education, BMI, lung medication, chronic diseases, smoking and physical activity), although this was not true in men; they further speculated this could be due to severity of depression as depression was associated with worse lung function.

In summary, there were two studies using other antidepressants with significant associations that assessed spirometry (one pre/post comparison, one crossover; average sample size=47); one non-significant study (RCT; sample size=12), and one study in the unexpected direction (cohort; sample size 2258). Regardless of significance, for the two studies that reported quantitative spirometric outcomes, the average effect of other antidepressants on FEV1 (in liters) was 0.04 (range: -0.08 to 0.16). One study used FEV1 as a percent of predicted and the average difference reported was 5.3%.

Overall, there were 21 studies with spirometry as an outcome, nine (43%) of these showed a significant association with antidepressants and improved spirometry. For selective serotonin reuptake inhibitors, 40% of the studies had a significant effect, with an average difference in FEV1 of 0.16 (range: 0.1 to 0.21) between those on and off selective serotonin reuptake inhibitors. For tricyclic antidepressants, 42% of the studies had a significant effect, with an average difference in FEV1 of 0.35. While firm conclusions cannot be drawn, so far there is no strong, consistent evidence that selective serotonin reuptake inhibitors positively improve spirometric outcomes.

### *Dyspnea*

#### *Selective serotonin reuptake inhibitors (Table 2.3, Column A)*

Six of the selective serotonin reuptake inhibitor studies included dyspnea as an outcome; the same two (33%) studies that found an association with spirometry also found one with dyspnea [45, 59]. In the study by Perna et al., six participants treated with citalopram had a decrease in their dyspnea scale from  $7.7 \pm 1.4$  to  $3.5 \pm 1.4$  ( $p < 0.05$ ) [45]. In the study by Momtaz et al., the treatment group had a decrease in their dyspnea scale from  $4.36 \pm 0.99$  to  $3.68 \pm 1.09$  ( $p = 0.001$ ); the group that did not receive treatment had an increase their dyspnea scale ( $4.50 \pm 1.01$  to  $5.17 \pm 0.99$ ,  $p = 0.001$  [59]).

In the study by Lacasse et al., the authors reported that unadjusted changes in the Chronic Respiratory Questionnaire at follow-up showed results favoring the hypothesized effect of selective serotonin reuptake inhibitors on reducing dyspnea, however this did not reach statistical significance; tabular results are not reported, but numeric results were displayed graphically [57]. In the study by Brown et al., there were no significant differences between the treatment and placebo groups for the change in ratings on the asthma control questionnaire ( $-7.1 \pm 7.6$  vs.  $-8.5 \pm 10.1$ ,  $p=0.47$ ) [61]. The later study by Brown et al. also reported no improvements in the asthma control questionnaire scores [60].

In summary, there were two studies using selective serotonin reuptake inhibitors with significant associations that assessed dyspnea (one cohort and one pre/post comparison; average sample size=31); four non-significant studies (one cohort and three RCTs; average sample size=41). An average effect for antidepressants on dyspnea could not be assessed since each study used a different method to assess dyspnea and these scales are not comparable (i.e. some range from 0-100 and some from 0-10) resulting in a wide range of effect estimates. Additionally, pooled effect estimates with methods such as Cohen's  $d$  were not feasible given the small sample sizes.

#### *Tricyclic antidepressants (Table 2.3., Column B)*

In total, there were four studies that assessed dyspnea involving tricyclic antidepressants [62, 63, 68, 69], only one (25%) of them showed a significant effect [69].

As mentioned earlier, Sugihara et al. did not report specific results or discriminate between spirometry and dyspnea outcomes, they only reported that 62% of participants had an excellent or good therapeutic effect [69]. Borson et al. also noted that antidepressant treatment was associated with a small improvement in dyspnea in their RCT, however this was only during activities requiring little energy (differential treatment effect:  $0.37 \pm 0.28$ ,  $p=0.04$ ) [62], but overall there was no change. The other two studies reported no impact of antidepressants on the dyspnea score. Carroll et al. noted that there was no statistical difference in the visual analog scale completed by participants; however, a small increase was noted during the placebo arm when the same scale was completed independently by the participants' spouse [63]. The median visual analog scale registered by the spouse was 47 (range 34-82) at entry, 54 (range 35-77) on placebo, and 46 (range 12-68) on protriptyline ( $p<0.01$ ).

In summary, there was one study using tricyclic antidepressants that noted significant associations with spirometry (pre/post comparison; average sample size=60) and three non-significant studies (two crossover and one RCT; average sample size=27).

#### *Other antidepressants (Table 2.3., Column C)*

Only one study assessed dyspnea using other antidepressants, the study by Grove et al. In their RCT of 12 individuals with COPD, the authors reported that the Borg score for perceived exertion on a 6-minute walk test was unchanged (Borg scale at baseline: 12; placebo: 12.5, treatment: 12.5) [75].

In summary, there were 11 studies that assessed dyspnea as an outcome, three (27%) of these found a significant association between antidepressants and decreased dyspnea. For selective serotonin reuptake inhibitors, 33% of the studies had a significant effect; for tricyclic antidepressants, 25% of the studies had a significant effect. As with spirometric outcomes, firm conclusions cannot be drawn but there is no strong, consistent evidence that selective serotonin reuptake inhibitors positively improve dyspneic outcomes.

We will now assess the study quality for methodological limitations.

## **STUDY QUALITY**

Although 12 (50%) of the studies were randomized controlled trials or randomized crossovers, there were important methodological limitations across the studies (**Table 2.5**). Fifty-four percent of the studies had unclear, incomplete follow-up of participants or unbalanced attrition between the treatment and control groups (detailed results on attrition for all studies are presented in **Appendix Table 4**). A quarter of studies measured and analyzed an outcome of interest, but did not completely report the results. Lastly, approximately a third of studies failed to control for important confounders or had inadequate measurement and testing of confounders. Detailed assessment for each study on the risk of bias assessment is presented in

## **POTENTIAL EFFECT MODERATORS**

### *Spirometry*

#### *Selective serotonin reuptake inhibitors*

There are some possible methodological explanations for the discrepancies between significant and non-significant selective serotonin reuptake inhibitor studies. The sampling for the non-significant studies all came from outpatient populations compared with inpatient or unknown populations for the significant studies. If the outpatient population was healthier (with a resulting higher lung function) than the inpatient population, this would produce an effect towards the null. Unfortunately, we are unable to compare the baseline FEV1 of the significant and non-significant studies since it was not reported for all; but among those that did report it, the non-significant studies had slightly higher lung function. All non-significant studies included participants with depression, while significant studies included both participants with and without comorbid depression. Including participants with comorbid depression would shift the effect towards the null if the inflammation seen in depression were hampering the effect of the antidepressants on lung function. Since the participants with depression have increased inflammation, they may need a higher dose to see an effect. There was a large amount of attrition in two of the studies that were non-significant [78]. Paroxetine was originally used in both Eiser et al.'s studies, in the cohort study and in the crossover study [78]. In the crossover study, four participants developed significant side effects on paroxetine and finished the study on lofepramine 140 mg in a single-blind fashion; in the cohort study, two participants switched to dothiepin 150 mg daily. Lofepramine and dothiepin are tricyclic antidepressants; if our hypothesis is true and selective serotonin reuptake inhibitors are more effective than other antidepressants, switching antidepressants during the trial would shift the effect towards the null and towards the intent to treat estimate.

In terms of the selective serotonin reuptake inhibitor used, the significant studies used citalopram and fluoxetine while the non-significant studies used sertraline or paroxetine. We have not seen any

literature that compares these specific drugs concerning lung function, but this is something to note and a possibility for future research.

### *Tricyclic antidepressants*

As with selective serotonin reuptake inhibitors, there are some potential methodological reasons for the discrepancies between significant and non-significant tricyclic studies. One of these is inconsistent dosing during the study. Series et al. reduced the dose of protriptyline to 10 mg a day after 2 weeks of therapy in two participants because of severe dryness of the mouth [66]; the other Series et al. study reported using a range of dosing (10-20 mg [67]). In Gordon et al., the investigators used the maximum tolerated dose or 100 mg [64]; Light et al. also used various doses of doxepin (150 mg max, if side effects occurred dosing was decreased) [65]. In contrast, the large majority of the significant tricyclic antidepressant studies reported using consistent dosing. The exception to this was Sugihara et al. who used 20-40 mg of amitriptyline; researchers discontinued the drug if symptoms were aggravated and increased it if there was no response [69]. Changing the dosing levels (especially lowering them) may result in a decreased response but is likely more representative of the effectiveness in clinical practice.

The baseline FEV1 of significant studies was double that of non-significant studies, but still below normal. The average age of the participants is approximately 40 years older in the non-significant studies than the significant studies. This is likely linked to the disease of the participants since three of the significant studies enrolled cystic fibrosis participants, a disease seen in youth, and all of the non-significant studies enrolled COPD participants, who are typically older. The significant studies had a larger median sample size (34 vs 16 participants). Additionally, the significant studies did not specifically include participants with depression while some of the non-significant studies did. Lastly, it was interesting to note that all of the significant studies employed amitriptyline, while the non-significant studies used protriptyline, doxepin, desipramine, or nortriptyline.

### *Other antidepressants*

Similar to studies of tricyclic antidepressants and selective serotonin reuptake inhibitors, the average sample size of the significant studies assessing other antidepressants was higher than the non-significant study and included both participants with and without depression. Furthermore, the baseline

FEV1 reported in the non-significant study by Grove et al. was 29% [75], which is categorized as very severe COPD according to the GOLD criteria [8]. These participants are very sick so it is not surprising that a low dose of mianserin did not produce an effect. There was one cross-sectional study; interestingly this was the only study that found an effect in the unexpected direction [77]. Unfortunately, parameters such as pre-treatment FEV1 were not reported so it is unknown if this had an effect on study outcome. However, this study did include participants with depression and had a very large sample size (2,258 participants). Unfortunately, the type of antidepressant was not given and the authors did not provide information on how common each antidepressant type was nor any heterogeneity of the association by antidepressant type.

Overall, across antidepressant types, there was no clear commonality among statistically significant studies. Notably, selective serotonin reuptake inhibitors did not stand out as more strongly associated with lung function improvements compared with tricyclic antidepressants or other antidepressants.

### *Dyspnea*

#### *Selective serotonin reuptake inhibitors*

Similar methodological discrepancies found in studies assessing spirometry were seen in studies assessing dyspnea (**Table 2.3.A and B, Column A**). The non-significant studies [57, 60, 61] all reported increasing the dose as tolerated, in contrast to the significant studies which kept participants on continuous doses. Both studies by Brown et al. [60, 61] increased the dosage for those who showed no response to the drug, and Lacasse et al. used 20 mg or the highest dose not associated with any side effect [57]. As with studies assessing spirometry, all of the non-significant studies included participants with depression while significant studies were mixed. All significant studies used the modified Borg scale to assess dyspnea. The non-significant studies used the asthma control questionnaire, a daily diary card of dyspnea on a 5-point scale, or the chronic respiratory questionnaire. The Borg scale is typically used during physical activities, such as walking or exercising; it is feasible that in order for the participants to notice a difference in their dyspnea, they need to exert themselves and be a little out of breath.

### *Tricyclic antidepressants*

Since there is only one study that showed a significant result (**Table 2.3. A and B, Column B**), sound conclusions could not be made on the methodological differences; however, we still compare differences across all studies below.

The significant study by Sugihara et al. was a cohort study with 60 participants (both in and out patients) [69]. In contrast, the non-significant studies were either crossovers or randomized controlled trials, with an average sample size of 27 out patients. We were unable to compare the baseline FEV1 or mean age of the participants, as it was not reported in Sugihara et al. Interestingly, as with the tricyclic antidepressant studies investigating spirometric outcomes, the significant study used amitriptyline, while the non-significant studies used protriptyline or nortriptyline.

### *Other antidepressants*

There was only one study of other antidepressants that had an outcome of dyspnea (non-significant) [75], therefore there are no comparisons to be made (**Table 2.3. A and B, Column C**). The limitations of this study, including enrolling participants who are classified as very severe COPD, have been discussed earlier in the spirometry section.

Across the dyspnea and spirometric outcomes, the majority of these studies are subject to methodological limitations and thus require caution in their interpretation.

## **DISCUSSION**

To our knowledge, this is the first systematic review of the literature on the effect of antidepressants on lung function. Our extensive literature search across multiple electronic databases revealed only 24 studies eligible for inclusion in this review.

We showed that the currently available published studies do not consistently support the hypothesized association between antidepressants and increased lung function. Specifically, 38% of studies had results that were significant and in the hypothesized direction, 58% non-significant, and 4% in the opposite (unexpected) direction. Results tended to vary by inclusion of participants with depression,

severity of baseline lung function impairment, and type of antidepressant. The inconsistent association may be because antidepressants truly are not advantageous for lung function, but it could also be due to the small sample sizes (median n=23), poor and inconsistent confounder control (1/3 of studies), and lack of complete reporting across studies. In order to elucidate if a true association exists, further research is needed properly controlling for key variables [80] such as baseline FEV1 and implementing suitable methodology such as accounting for change/switch in antidepressant type.

Since all but two [70, 77] of the studies were performed in controlled environments where researchers closely monitored or interacted with the participants, the effectiveness of antidepressants on lung function is not well established in the real world. Real-world applicability includes participants being adherent to the treatment regime. An important consideration of this is that over half of the studies had significant attrition or uneven attrition between the control and treatment groups, a common reason being side effects of the drug. Thirty-eight percent of selective serotonin reuptake inhibitor studies had significant differential attrition compared with 58% of tricyclic antidepressant studies, suggesting that tricyclic antidepressants have worse side effects than selective serotonin reuptake inhibitors [81].

More research is needed using population-based data to provide information on the potential for certain antidepressants in improving lung function. For example, all but one study [77] had sample sizes with less than 91 participants, with the large proportion (46%) having less than 20 participants. Only one large cohort study was found, and the authors did not report the antidepressant type of the participants. Combined with the significant attrition in a large portion of the studies, many outcomes were based on very small sample sizes. In order to enhance knowledge on the potential effects of antidepressants on lung function, a large, well-measured dataset is needed.

In summary, while individual studies showed statistical and clinical improvement in lung function, overall there was no strong evidence for the use of antidepressants as a whole, or specifically selective serotonin reuptake inhibitors, to improve lung function. There was large variation in results and, while potential effect modifiers were noted, no single parameter stood out as being consistently different between significant and non-significant studies. However, this may be due to the small sample sizes used and lack of complete data reported. Given the small sample sizes noted, null findings aren't unexpected. However,

when assessing the average effect of selective serotonin reuptake inhibitors on spirometry, the average difference in FEV1 between those on and off selective serotonin reuptake inhibitors was 0.09 (range -0.01 to 0.21). This small change is unlikely to represent a clinically meaningful or symptomatic difference for the individual.

This review has several limitations. First, the study results were categorized according to the direction and significance of effect, potentially overemphasizing the importance of statistical significance. Given the restrictions in the details published, this approach was considered acceptable, despite the limitations. An additional limitation was that many studies did not report complete information, leading to high assessments for risk of bias; for example, categorizing failure to report baseline FEV1 as high risk may overestimate risk. Future reviews could be enhanced by obtaining additional information from the study authors. Lastly, this review relied on a single screening interpretation, is therefore subject to error, and can be refined through additional quality control measures and coauthor input in the future.

Overall, more research is needed, specifically in population-based models, to assess the effectiveness of antidepressants in improving lung function. Researchers should consider controlling for lung function impairment, type of antidepressant, comorbid depression, and sociodemographic variables.

## TEXT FIGURES AND TABLES

Figure 2.1. Flow chart of studies included in systematic literature review

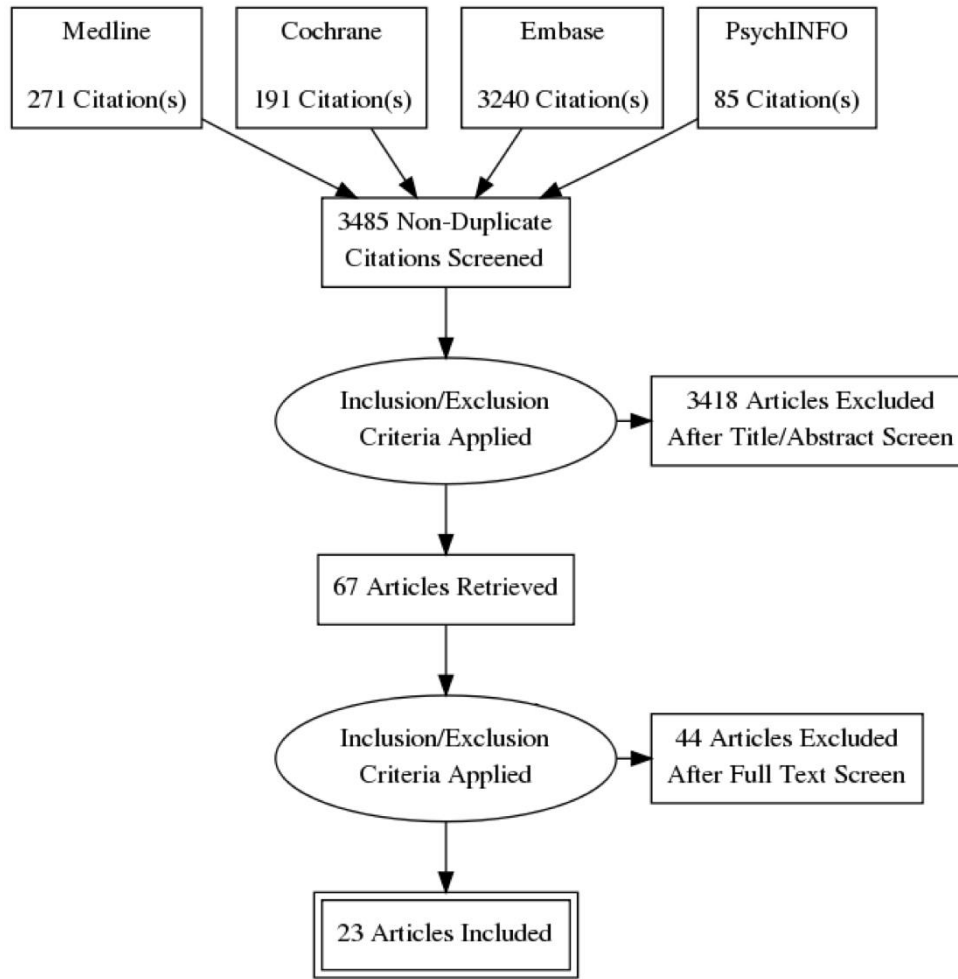


Table 2.1. Characteristics of the twenty-four studies included, stratified by antidepressant type

		A. SSRI	B. TCA	C. Other	Total
		N (%) or Mean±SD	N (%) or Mean±SD	N (%) or Mean±SD	N (%) or Mean±SD
Studies (%)		8 (33%)	12 (50%)	4 (17%)	24 (100%)
Study design (text):	Cohort	3 (37.5%)	4 (33.3%)	1 (25%)	7 (29%)
	Crossover	1 (12.5%)	5 (42%)	2 (50%)	8 (33.3%)
	RCT	4 (50%)	2 (16.7%)		5 (21%)
	Other		1 (8%)	1 (25%)	2 (8%)
Sample size:	1-20	2 (25%)	7 (58%)	2 (50%)	11 (46%)
	21-40	4 (50%)	4 (33%)		8 (33%)
	>40	2 (25%)	1 (8%)	2 (50%)	5 (21%)
Sampling:	In-patient	1 (12.5%)			1 (4%)
	Out-patient	6 (75%)	10 (83%)	4 (100%)	20 (83%)
	Both in & out patient		1 (8%)		1 (4%)
	Unknown	1 (12.5%)	1 (8%)		2 (8%)
Duration:	Cross sectional			1 (25%)	1 (4%)
	<1 wk-4 wks	1 (12.5%)	3 (25%)	2 (50%)	6 (25%)
	5-10 wks	2 (25%)	4 (33%)		6 (25%)
	11 wks -<1 yr	5 (62.5%)	3 (25%)		8 (33%)
	≥ 1 yr		2 (16.7%)	1 (25%)	3 (12.5%)
Population:	No respiratory problems			2 (50%)	2 (8%)
	COPD	6 (75%)	7 (58%)	1 (25%)	14 (58%)
	CF		3 (25%)		3 (12.5%)
	Asthma	2 (25%)	2 (17%)	1 (25%)	5 (21%)
Baseline FEV <sub>1</sub> :	Liters	1.1±0.5	1.0±0.3	3.6±0.7	1.2±0.4
	% predicted	56.1±28.7	49.9±13.1	82.5±10.1	51.4±13.3
	Unknown, n (%)	3 (37.5%)	1 (8%)	2 (50%)	6 (25%)
% female:	0-25%		1 (8%)	1 (25%)	2 (8%)
	26-50%	3 (37.5%)	7 (58%)	2 (50%)	12 (50%)
	51-75%	2 (25%)	3 (25%)	1 (25%)	6 (25%)
	76-100%	1 (12.5%)			1 (4%)
	Unknown, n (%)	2 (25%)	1 (8%)		3 (12.5%)
Mean age:		59.5±7.8	48.7±7.8	37.0±1.8	49.8±7.2
	Unknown, n (%)	2 (25%)	2 (16.7%)		4 (16.7%)
Participants with comorbid depression:	Yes	7 (87.5%)	2 (16.6%)	2 (50%)	11 (45.8%)
	No	1 (12.5%)	10 (83.3%)	2 (50%)	13 (54.2%)

SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; RCT: randomized controlled trial; COPD: chronic obstructive pulmonary disease; CF: cystic fibrosis; wk: week; yr: year

Table 2.2.A. Spirometry study results by antidepressant type

		A. SSRI			B. TCA			C. Other			
		Sig.	Non-sig.	Total	Sig.	Non-sig.	Total	Sig.	Non-sig.	Unexpected	Total
<i>Overall results (%)</i>		2 (40%)	3 (60%)	5 (24%)	5 (42%)	7 (58%)	12 (57%)	2 (50%)	1 (25%)	1 (25%)	4 (19%)
Study design:	Cohort	2 (50%)	2 (50%)	4 (80%)		2 (50%)	2 (16.7%)			1 (100%)	2 (50%)
	Crossover		1 (100%)	1 (20%)	1 (20%)	4 (80%)	5 (42%)	1 (100%)			1 (25%)
	RCT				1 (50%)	1 (50%)	2 (16.7%)		1 (100%)		1 (25%)
	Other				3 (60%)		3 (25%)	1 (100%)			
Sample size:	Average	28	25	25	34	16	19	47	12	2258	47
	1-20	1 (50%)	1 (50%)	2 (40%)	2 (28.5%)	5 (71%)	7 (58%)	1 (50%)	1 (50%)		2 (50%)
	21-40		2 (100%)	2 (40%)	2 (50%)	2 (50%)	4 (33%)				
	>40	1 (100%)		1 (20%)	1 (100%)		1 (8%)	1 (50%)		1 (50%)	2 (50%)
Sampling:	In-patient	1 (100%)		1 (20%)							
	Out-patient		3 (100%)	3 (60%)	4 (40%)	6 (60%)	10 (83%)	2 (67%)	1 (33%)	1 (100%)	4 (100%)
	In & out patient				1 (100%)		1 (8%)				
	Unknown	1 (100%)		1 (20%)		1 (100%)	1 (8%)				

Table 2.2.B. Spirometry study results by antidepressant type

Moderators of effect											
Baseline FEV <sub>1</sub> :	Liters	1.0±0.4	1.1±0.6	1.1±0.5	2.0	0.9±0.4	1.0±0.3	3.6±0.7			3.6±0.7
	% predicted		43±16	43±16	62.1±18.6	31.6±4.9	49.9±13.1	107±14	29±3.2%		82.5±10.1
	Unknown		1 (100%)	1 (33%)	1 (100%)		1 (8%)	1 (50%)		1 (50%)	2 (50%)
% female:		33.7	50	39.1	49.4	35.1	41.5	44.5	25	65.2	44.8
	Unknown		2 (100%)	2 (40%)		1 (100%)	1 (8%)				
Mean age:		65.5±3.0	68±8	66.3±4.7	28.6±9.3	72.2±7.3	48.7±7.8	22.3	62.5±1.5	41.1	37.0±1.8
	Unknown		2 (100%)	2 (40%)	1 (50%)	1 (50%)	2 (16.7%)				
Duration:	Average	8 weeks	8 weeks	8 weeks	17 weeks	17 weeks	17 weeks	27	3	Cross-sectional	19
Study Design:	Cross-sectional									1 (100%)	1 (25%)
	<1 wk-4 wks	1 (100%)		1 (20%)	2 (67%)	1 (33%)	3 (43%)	1 (50%)	1 (50%)		2 (50%)
	5-10 wks		2 (100%)	2 (40%)		4 (100%)	4(33%)				
	11 wks <-1 yr	1 (50%)	1 (50%)	2 (40%)	2 (67%)	1 (33%)	3 (25%)				
	≥ 1 yr				1 (50%)	1 (50%)	2 (16.7%)	1 (50%)			1 (25%)
Participants w/ depression:	Yes	1 (25%)	3 (75%)	4 (80%)		2 (100%)	2 (16.6%)	1 (50%)		1 (50%)	2 (50%)
	No	1 (100%)		1 (20%)	5 (50%)	5 (50%)	10 (83.3%)	1 (50%)	1 (50%)		2 (50%)
Antidepressant:	Citalopram	1 (100%)		1 (20%)							
	Sertraline		1 (100%)	1 (20%)							
	Paroxetine		2 (100%)	2 (40%)							
	Fluoxetine	1 (100%)		1 (20%)							
	Amitriptyline				5 (100%)		5 (42%)				
	Protriptyline					4 (100%)	4 (33.3%)				
	Doxepin					1 (100%)	1 (8%)				
	Desipramine					1 (100%)	1 (8%)				
	Nortriptyline					1 (100%)	1 (8%)				
	Tianeptine							1 (100%)			1 (25%)
	Mianserin								1 (100%)		1 (25%)
	Various							1 (50%)		1 (50%)	2 (50%)

SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; RCT: randomized controlled trial; wk: week; yr: year; sig: significant

Table 2.3.A. Dyspnea study results by antidepressant type

		A. SSRI			B. TCA			C. Other	
		Sig.	Non-sig.	Total	Sig.	Non-sig.	Total	Non-sig.	Total
<i>Overall results (%)</i>		2 (33%)	4 (67%)	6 (55%)	1 (25%)	3 (75%)	4 (36%)	1 (100%)	1 (9%)
Study design:	Cohort	1 (50%)	1 (50%)	2 (33%)					
	Crossover					2 (100%)	2 (50%)		
	RCT		3 (100%)	3 (50%)		1 (100%)	1 (25%)	1 (100%)	1 (100%)
	Other	1 (50%)		1 (17%)	1 (100%)		1 (25%)		
Sample size:	Average	31	41	36	60	27	35	12	12
	1-20	1 (100%)		1 (17%)		1 (100%)	1 (25%)	1 (100%)	1 (100%)
	21-40		3 (100%)	3 (50%)		2 (100%)	2 (50%)		
	>40	1 (50%)	1 (50%)	2 (25%)	1 (100%)		1 (25%)		
Sampling:	In-patient	1 (100%)		1 (17%)					
	Out-patient		5 (100%)	5 (83%)		2 (100%)	2 (50%)	1 (100%)	1 (100%)
	Both in & out patient				1 (100%)		1 (25%)		
	Unknown	1 (100%)		1 (17%)		1 (100%)	1 (25%)		

Table 2.4.B. Dyspnea study results by antidepressant type

Moderators of effect									
Baseline FEV <sub>1</sub> :	Liters	1.0±0.4	1.1±0.6			0.69±0.41			
	% predicted		34.6±20.7			22.3±6.0		29±3.2%	29±3.2%
	Unknown, n (%)		2 (100%)	2 (33%)	1 (100%)		1 (25%)		
% female:		33.7	56.7		31.6	43.7		25	25
	Unknown, n (%)								
Mean age:		65.5±3.0	52.6			61.2		62.5±1.5	62.5±1.5
	Unknown, n (%)		1 (100%)	1 (17%)	1 (100%)		1 (25%)		
Duration:	Average	10 weeks	12 weeks	11 weeks	16 weeks	9 weeks	11 weeks	3 weeks	3 weeks
	Cross sectional								
	<1 wk-4 wks	1 (100%)		1 (17%)				1 (100%)	1 (100%)
	5-10 wks					2 (100%)	2 (50%)		
	11 wks -<1 yr	1 (20%)	4 (80%)	5 (83%)	1 (50%)	1 (50%)	2 (50%)		
	≥ 1 yr								
Participants with depression:	Yes	1 (20%)	4 (80%)	5 (83%)		2 (100%)	2 (50%)		
	No	1 (100%)		1 (17%)	1 (50%)	1 (50%)	2 (50%)	1 (100%)	1 (100%)
Antidepressant:	Citalopram	1 (50%)	1 (50%)	1 (17%)					
	Paroxetine		2 (100%)	2 (33%)					
	Fluoxetine	1 (50%)	1 (50%)	2 (33%)					
	Escitalopram								
	Amitriptyline				1 (100%)		1 (25%)		
	Protriptyline					2 (100%)	2 (50%)		
	Nortriptyline					1 (100%)	1 (25%)		
	Mianserin							1 (100%)	1 (100%)
SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; RCT: randomized controlled trial; wk: week; yr: year; sig: significant									

Table 2.5. Overview of study quality, stratified by antidepressant type

		<b>A. SSRI</b>	<b>B. TCA</b>	<b>C. Other</b>	<b>Total</b>
		8 (33%)	12 (50%)	4 (17%)	24 (100%)
Study participation:	High	1 (13%)	3 (25%)		4 (17%)
	Low	7 (87%)	9 (75%)	4 (100%)	20 (83%)
	Unclear				
Study Attrition:	High	3 (38%)	7 (58%)		10 (42%)
	Low	3 (38%)	5 (42%)	3 (75%)	11 (46%)
	Unclear	2 (25%)		1 (25%)	3 (12%)
Outcome Measurement and Reporting:	High	2 (25%)	2 (17%)	2 (50%)	6 (25%)
	Low	6 (75%)	10 (83%)	2 (50%)	18 (75%)
	Unclear				
Study Confounding:	High	3 (38%)	3 (25%)	1 (25%)	7 (29%)
	Low	5 (62%)	9 (75%)	3 (75%)	17 (71%)
	Unclear				
SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; High indicates high risk of bias					

## CHAPTER 3. A POPULATION BASED STUDY OF THE ASSOCIATION BETWEEN SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND CONCURRENT LUNG FUNCTION

### ABSTRACT

*Background:* COPD refers to a group of inflammatory diseases that cause airflow obstruction, respiratory muscle weakness, and breathing-related problems (such as increased breathlessness, frequent coughing, and tightness in the chest) that result in reduced lung function. Some antidepressants, namely selective serotonin reuptake inhibitors, may have potential off-label uses in treating COPD symptoms. *Objectives:* This study aims to investigate whether participants taking selective serotonin reuptake inhibitors have better concurrent lung function than those not taking selective serotonin reuptake inhibitors. *Methods:* Analyses were conducted using exam 4 and 5 data from the Multi Ethnic Study of Atherosclerosis-Lung Study. Participants brought to the exam visit containers for all medications taken during the prior two weeks. Different antidepressants were categorized according to the Anatomical Therapeutic Chemical classification system. Lung function and patient symptoms were assessed through two measures: spirometry and dyspnea ratings. Included confounders consisted of smoking status, pack-years and depressive symptoms. We used two different approaches to analyzing the data, linear regression and difference-in-difference analyses. *Main results:* There were 3,542 eligible participants at exam 4 and 2,954 participants at exam 5. At both exams, findings indicate an inverse relationship between selective serotonin reuptake inhibitors and FEV1%, contrary to our hypothesis. Selective serotonin reuptake inhibitors were also significantly associated with a higher odds of dyspnea. The difference-in-difference analysis revealed that those who went on selective serotonin reuptake inhibitors decreased their lung function while those who remained off increased their lung function for a net effect of 4.0% ( $p=0.03$ ). Results do not support hypothesized associations between selective serotonin reuptake inhibitors and improved lung function. *Conclusions:* The overall results suggest selective serotonin reuptake inhibitors do not positively affect lung function or dyspnea.

## INTRODUCTION

COPD refers to a group of diseases that cause airflow obstruction, respiratory muscle weakness, and breathing-related problems (such as increased breathlessness, frequent coughing, and tightness in the chest) that result in reduced lung function [8]. Middle-aged and older adults are most likely to have a diagnosis of COPD. Worldwide, COPD affects men and women equally. Symptoms include shortness of breath (or dyspnea), persistent (chronic) cough, wheezing and labored breathing during physical activity. Respiratory exacerbations, a sudden worsening of respiratory symptoms and airway function, are also a concern for COPD patients and their practitioners. Currently, there is no cure for COPD; therefore, practitioners focus on reducing the risk of respiratory exacerbations and mortality and improving symptoms as the primary treatment goals [11].

Inflammation plays a large role in COPD, as evidenced by the Global Initiative for Chronic Obstructive Lung Disease classifying COPD as an inflammatory disease [8]. The inflammatory markers found in older adults with stable COPD [5, 82] reflect disease severity and functional status. However, even in young adults without COPD, and independent of asthma, smoking, and body weight, an inverse association is seen between lung volumes and systemic inflammation [83]. This association of higher inflammatory markers with lower lung function in those without COPD suggests an association between lung function and inflammation predating the clinical development of obstructive disease. Therefore, reducing inflammation may be beneficial for subclinical disease, in addition to those with clinically defined obstructive disease.

Since inflammation is relevant to COPD symptoms, current treatments for low function are designed to decrease inflammation [12-15]. For example, due to their anti-inflammatory effects, inhaled corticosteroids improve pulmonary function and dyspnea, shorten hospitalizations, and decrease the frequency of exacerbations [21, 22]. However, they also result in significant adverse outcomes, which lead researchers to consider other drugs. Statins, approved as lipid-lowering agents, are potentially useful in COPD due to their anti-inflammatory effects, as evidenced by observational studies showing that statins reduce COPD mortality and inflammatory biomarkers [28-30].

Like statins, some antidepressants, namely selective serotonin reuptake inhibitors, may have off-label uses in treating COPD symptoms. Selective serotonin reuptake inhibitors are anti-inflammatory and act upon serotonin, which is integral to central breathing control [16, 17]; this combination may provide an additional benefit over current COPD treatment regimes.

#### *Prior research on antidepressants & lung function*

Several small studies have examined the effect of antidepressants on lung function. A recent review showed that the currently available published studies do not consistently support the hypothesized association. Only 38% of studies observed a significant positive association between antidepressants and lung function (Chapter 2). Of the remaining studies, 46% found a non-significant association regardless of the direction and 4% found a significant result in the opposite direction as hypothesized. Results tended to vary by inclusion of participants with comorbid depression, severity of lung function impairment, and type of antidepressant. However, the majority of the studies were subject to methodological limitations including small sample sizes, poor or inconsistent confounder control, and lack of complete reporting across studies. Given the plausibility of a mechanism of action and the limitations of previous studies, more research is needed using population-based data to provide information on the potential for certain antidepressants in improving lung function.

## **PURPOSE**

The purpose of this study is to investigate whether participants on selective serotonin reuptake inhibitors have better concurrent lung function than those not selective serotonin reuptake inhibitors. It aims to help augment the limited evidence on the effect of selective serotonin reuptake inhibitors on lung function. This paper estimates the effect of selective serotonin reuptake inhibitors on lung function, after adjusting for potential confounders, in a large population based sample of adults.

## **METHODS**

*Sample: The Multi Ethnic Study of Atherosclerosis-Lung Study*

Sponsored by the National Heart Lung and Blood Institute, the Multi Ethnic Study of Atherosclerosis (MESA) is a multi-center, population-based, longitudinal study of 6,814 men and women aged 45-64 years at baseline across six sites in the United States (Columbia University, New York; Johns Hopkins University, Baltimore; Northwestern University, Chicago; UCLA, Los Angeles; University of Minnesota, Twin Cities; Wake Forest University, Winston Salem) (ClinicalTrials.gov Identifier: NCT00005487) [84]. MESA investigates the prevalence, correlates, and progression of subclinical cardiovascular disease and risk factors that predict progression to clinical cardiovascular disease. Exclusion criteria consisted of clinical cardiovascular disease (physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, or angina), current atrial fibrillation, any cardiovascular procedure, pregnancy, active cancer treatment, weight greater than 300 pounds, a serious medical condition which preclude long term participation, nursing home residence, cognitive inability, inability to speak English, Spanish, Cantonese, or Mandarin, plans to leave the community within five years, and a chest CT within the past year. At baseline, approximately 38% of the recruited participants were White, 28% Black, 22% Hispanic, and 12% Asian, predominantly of Chinese descent. A full description of the objectives and design has previously been published [84].

As illustrated in **Figure 3.1**, the first MESA exam visit was from July 2000-August 2002 and was followed by four follow-up exams: September 2002-February 2004, March 2004-September 2005, September 2005-May 2007, and April 2010-December 2011. The MESA protocol, including information about the source populations from which recruitment occurred, further details on exclusion criteria, and other information, is available at [www.mesa-nhlbi.org](http://www.mesa-nhlbi.org). A description of the cohort at exams 1-5, study timeline, and procedures related to this study are in

**Appendix Table 6 and Appendix Table 7.**

MESA-Lung is an ancillary study of MESA to test the endothelial hypothesis of COPD and emphysema (ClinicalTrials.gov Identifier: NCT00843271). The biological hypothesis that underlies the MESA-Lung Study is that alterations in endothelial and vascular function are associated with the pathogenesis and progression of subclinical COPD and emphysema, in part through the effects of systemic inflammation on the vascular endothelium.

In 2004-2006, the MESA-Lung study recruited 3,965 participants sampled randomly from MESA exam 3 and 4 participants who had baseline flow-mediated dilatation measures (89% of MESA participants), attended MESA exam 3 or 4 (87% of MESA participants), and consented to genetic analyses (99% of MESA participants). The MESA-Lung cohort is approximately 35% White, 24% Black, 23% Hispanic, and 18% Asian, mostly of Chinese descent. Of the original MESA-Lung cohort, over 3,000 were re-examined in 2010-2012 (MESA-Lung 2). Our analyses use the MESA-Lung data 1 and 2 (which corresponds to MESA exam 3, 4 and 5). The institutional review boards of all collaborating institutions and the National Heart Lung and Blood Institute (National Institutes of Health, Bethesda, MD, USA) approved the protocols of MESA and all procedures described herein. All participants provided informed consent. The MESA publications and presentations committee approved a proposal for this analysis.

## **MEASURES**

### *Exposure variable*

The exposure of interest was use of antidepressants, specifically selective serotonin reuptake inhibitors. Participants brought to the exam visit containers for all medications taken during the prior two weeks. Different antidepressants were categorized according to the Anatomical Therapeutic Chemical classification system (selective serotonin reuptake inhibitors, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors) [85]. We coded this variable as an indicator variable (yes (1)/no (0)) for each antidepressant class to indicate whether a participant was taking the drug or not at the time of the visit.

### *Outcome variables*

The outcome was lung function and patient symptoms, assessed through two measures: spirometry and dyspnea ratings. Spirometry assesses how well the lungs work by measuring how much air is inhaled, how much is exhaled, and how quickly the air is exhaled. Normal spirometry readings vary, depending on age, size and gender. If the airways are narrowed from obstruction, then the amount of air that can be exhaled is reduced. Spirometry can also help to assess if treatment opens the airways through an improvement in the readings. Dyspnea ratings measure the subjective experience of breathing discomfort. We assessed both because spirometry gives an objective assessment of lung function improvement while dyspnea gives a patient-centered outcome on how the patient feels. While it is important to know if the objective lung function improves, having patient-centric results is also important- it does not matter how much the lung function improves if the patient does not feel better. Spirometry is often used in diagnosing pulmonary disease since it is standardized and the current gold standard for objectively defining airflow obstruction [50]. In contrast, there are various questionnaires and scales used to measure dyspnea, making comparisons across studies challenging.

*Spirometry:* A decreased forced expiratory volume in one second (FEV1) is the measure primarily used to show reduced lung function in COPD [51]. Predicted reference values have been calculated and compared with samples of healthy subjects drawn from the general population to yield percent predicted (%) standards. While many different percent predicted standards exist, the American Thoracic Society uses an equation that gives referents based on height, age, gender, and race [86]. Spirometry was measured in the MESA-Lung study in accordance with American Thoracic Society/European Respiratory Society guidelines, [50, 87] on a dry-rolling-sealed spirometer (Occupational Marketing, Inc., Houston, TX) as previously described [88]. We used percent-predicted values (FEV1%) that are continuous in our analyses.

*Dyspnea:* Trained interviewers assessed dyspnea at both exams. We defined dyspnea as a positive answer to one of the following questions: “When walking on level ground, do you get more breathless than people your own age?” or “Do you ever have to stop walking due to breathlessness?” This definition corresponds to the modified Medical Research Council dyspnea scale grade 2 or worse [89]. Dyspnea was coded dichotomously (yes (1)/no (0)).

### *Hypothesized confounders*

To identify potential confounders and the minimal set necessary for control, we developed a directed acyclic graph based on previous literature (**Appendix Figure 1**). From the literature aided by the directed acyclic graph, we deemed health insurance, smoking status, and depressive symptoms to be potential confounders. We also considered age and gender, but since these variables are adjusted for in FEV1% equations we did not adjust for them in the analyses.

Health Insurance: Different health coverage results in different prescription coverage (some plans have better coverage of prescription drugs than others do). Additionally, lack of health insurance has been associated with a decline in overall health [90]. Health insurance was categorized as indicator variables for: None (referent group), Medicaid, Medicare, Private, and VA/Other.

Smoking status and pack-years: Smoking destroys the alveoli in the lungs, reducing lung function. Smoking is also linked to depression [91, 92]. Depression leads to antidepressant use. Smoking status was categorized into never (0), former (1) and current smokers (2), with never smokers as the referent group.

Pack-years is a measure of smoking duration and amount. Quantification of pack-years is important because increased tobacco exposure is closely associated with lower lung function [93, 94]. Additionally, depression is associated with increased pack-years [95].

Depressive symptoms: In epidemiologic studies, depression is associated with lower lung function [96]. One potential mechanism for this association is that those who are depressed put less effort forth on their spirometry tests, resulting in lower lung function scores. Additionally, depression is an indication for antidepressant medication. In MESA, the Centers for Epidemiologic Studies Depression (CES-D) scale [97], was used as a measure of depressive symptoms. The 20 items in the CES-D scale measure symptoms of depression: sadness, loss of interest, appetite, sleep, thinking/concentration, guilt, being tired, movement, and suicidal ideation. CES-D score was centered on the mean.

### *Analytic approach*

Analyses were conducted in SAS 9.4. We excluded participants if they a) did not have exposure (medication) information available, b) were on more than one antidepressant or c) were missing data on any confounder included in the model. See *Error! Reference source not found.*, *Error! Reference source not found.* for an explanation on this choice of handling missing data.

*Confounder selection:* Final selection of confounders included an observed association with the exposure and outcomes ( $p < 0.20$ ) in linear or logistic regression (depending on the dependent variable), and a change of 10% or more in the crude exposure-outcome (betas) [98] when the potential confounder was added to the crude model. To keep the models consistent between exams, confounders that were found to have a 10% change in the crude exposure-outcome in either exam 4 or 5 were used.

*Main analyses:* We used two different approaches in analyzing the data, linear regression and difference-in-difference analyses. The linear regression approach assesses the association of selective serotonin reuptake inhibitors on lung function at exam 4 and exam 5, separately, which allows us to see the average difference between the control and treatment groups. The difference-in-difference approach compares the effect of those who change their selective serotonin reuptake inhibitor status between exams 4 and 5 with those who do not. The advantage of also performing the difference-in-difference analysis is that it allows us to remove biases between groups that do not change overtime.

### *Linear regression models*

The effects of selective serotonin reuptake inhibitors are likely to be short-lived as the half-life of these drugs is limited, ranging from approximately 4-7 hours to about 4-6 days. Therefore, we would expect concurrent effects of selective serotonin reuptake inhibitors on lung function. It may be odd to expect this given that the effect of antidepressants on depression is slow [99]; however, antidepressants quickly stop the process of serotonin transporters from taking up released serotonin. In people with depression, G proteins build up and lose access to a molecule called cyclic AMP, which the proteins need in order to transmit the signals they get from serotonin and the reason behind the delayed effects of antidepressants on depression.

However, these G proteins are not involved in the pathways for lung function [100], so we would still expect to see immediate effects of selective serotonin reuptake inhibitors on lung function.

We examined selective serotonin reuptake inhibitors and lung function at exam 4 and at exam 5; FEV1% was normally distributed and analyzed using multiple linear regression, assumptions were checked by inspection of the residuals. Dyspnea was analyzed using logistic regression.

#### *Difference-in-Difference analysis*

The difference-in-difference technique aims at restructuring observational data to approximate an experimental design and accounts for the time-invariant effect of any measured or unmeasured person-level characteristic. We employed a difference-in-difference analysis comparing those who changed their selective serotonin reuptake inhibitor status (inconsistent status) between exam 4 and exam 5 with those who did not (consistent status). Because difference-in-difference models are a repeated measures design, the outcome values for a subject are assumed to be correlated. To account for this correlation, we used a repeated measures ANOVA (generalized estimating equations (GEE) for dyspnea); this allows us to account for the correlation within subjects and provides the mean outcome values in each exposure group for each exam [101].

As illustrated in **Table 3.1**, we stratified by selective serotonin reuptake inhibitor use at exam- those who were on selective serotonin reuptake inhibitors at exam 4 (Column A) and those who were not on selective serotonin reuptake inhibitors at exam 4 (Column C). The control and treatment groups were determined by the selective serotonin reuptake inhibitor status at exam 5 (Columns B and D). Those who had consistent status between exam 4 and 5 were the control group and those who switched were the treatment group. We repeated this for dyspnea, as a percentage of patients who reported dyspnea. If our hypothesis is supported, we would expect the treatment group in comparison group 1 to have a decrease in lung function compared with the control group; in comparison group 2, we would expect the treatment group to have an increase in lung function compared with the control group,

Although our interest is in selective serotonin reuptake inhibitors, we also investigated other classes of antidepressants to distinguish the effects of antidepressants that work through decreasing depression

and those that work through the biological pathways mentioned above (serotonin and inflammation). We hypothesized that the effects of selective serotonin reuptake inhibitors on lung function are due to their biological mechanisms as opposed to their effect on depression. If the other antidepressants also have a positive effect on lung function, then we will have less confidence that it is due to the biologic mechanisms rather than a reduction of depression symptoms.

#### *Corticosteroid analysis*

There are approximately 400 participants with COPD in the cohort. As inhaled corticosteroids and bronchodilators are the current medications for low lung function, we performed an additional analysis that included an indicator variable for common medications that affect lung function in the model (**Appendix Table 8**). The purpose of our analysis was to determine if our results remain when accounting for other medications that affect lung function.

## **RESULTS**

#### *Sample characteristics*

As seen in

**Table 3.2**, the MESA-Lung sample consisted of 3,542 eligible participants at exam 4. The mean age of the sample was 66 years, 51% were female, 35% White, 16% Asian, 26% Black, and 23% Hispanic. Approximately 9% were current smokers and 39% were former smokers, with an average of 22 pack-years. The mean FEV1%, was  $94 \pm 18\%$ ; dyspnea was reported in 15% of the cohort. The average CES-D score was eight, with 14% classified as depressed from the CES-D. We excluded 11 participants from further analysis since they were on more than one antidepressant and we would not be able separate out the effects of the antidepressants if they were on more than one concurrently.

At exam 4, 178 participants were on selective serotonin reuptake inhibitors, 42 on serotonin norepinephrine reuptake inhibitors, and 38 on tricyclic antidepressants. The average age was roughly similar across antidepressant groups, with those on tricyclic antidepressants being slightly older. The selective serotonin reuptake inhibitor group had the highest proportion of current smokers and the lowest FEV1% at baseline. This group also had the largest proportion of participants who were depressed.

As shown in **Table 3.3** there were 2,954 participants at exam 5. As expected, the mean age at exam 5 increased from exam 4 to 69 years. The demographic distribution was similar from exam 4 with the cohort being 51% female, 38% White, 14% Asian, 26% Black, and 21% Hispanic. Approximately 7% were current smokers and 39% were former smokers, with an average of 22 pack-years. Mean FEV1% was 95% with 15% of the population reporting dyspnea. The average CES-D score was eight, with 14% classified as depressed. We excluded 10 individuals from further analysis since they were on more than one antidepressant.

At exam 5, 152 participants were on selective serotonin reuptake inhibitors, 54 on serotonin norepinephrine reuptake inhibitors, and 25 on tricyclic antidepressants. The average age was similar between all groups. At this exam, the tricyclic antidepressant group had the highest proportion of patients who were current smokers and the lowest FEV1%. The selective serotonin reuptake inhibitor group still had the highest proportion of patients who were depressed.

### *Confounder criteria*

Before running any models, we tested the potential confounders to confirm their association with the exposure and outcome variables (

Table 3.4). At exam 4, all potential confounders were significantly associated with dyspnea and selective serotonin reuptake inhibitors. The only variable that was not significant with FEV1% was type of health insurance. Similar patterns of association were seen at exam 5 (see **Appendix Table 9**).

Next, we placed each confounder into the model with selective serotonin reuptake inhibitors and the outcomes to see if a 10% change in the crude exposure-outcome beta was seen. All confounders except for health insurance met this criterion and therefore were included in further analyses. We also looked at a model including health insurance and the estimates did not change, suggesting that the results were robust to the exclusion of this variable in further analyses.

#### *Linear regression models*

##### *Forced expiratory volume in one second*

The unadjusted and adjusted findings from the linear regression models between selective serotonin reuptake inhibitors and FEV1% are in **Table 3.5** and

**Table 3.6.** At both exams, findings indicate an inverse relationship between selective serotonin reuptake inhibitors and FEV1%, against our hypothesis. This association was moderately attenuated by the inclusion of confounders in the model, but still had a substantial negative association in the fully adjusted model (Column B) at exam 4 and exam 5.

When other antidepressants were added to the model (Column C), the associations remained consistent at exam 4 and were again in the same inverse direction at exam 5. Except for tricyclic antidepressants at exam 4, all antidepressants were inversely associated with FEV1% at both exams; however, these estimates were not very precise as evidenced by their wide confidence intervals.

We performed an analysis including a variable for medications that affect lung function in the models. At exam 4, 4.5% of participants were on these medications, with 9.4% on them at exam 5. When adding corticosteroid use to the adjusted linear regression model (Adjusted model 1 from tables 4 and 5), being on selective serotonin reuptake inhibitors was now associated with a -2.38 (95% CI: -4.94 to 0.17) lower FEV1% at exam 4 and a -1.11 (95% CI: -4.08 to 1.85) lower FEV1% at exam 5. For the logistic regression models, when adding the variable for lung function medications, being on selective serotonin reuptake inhibitors was now associated with a 1.23 (95% CI: 0.85 to 1.80) increased odds for dyspnea at exam 4 and a 1.25 (95% CI: 0.86 to 1.82) increased odds at exam 5.

### *Dyspnea*

The logistic regression models assessing the relationship between selective serotonin reuptake inhibitors and dyspnea are in **Table 3.7** and **Table 3.8**. Selective serotonin reuptake inhibitors were significantly associated with an increased odds of dyspnea in the unadjusted models; but after controlling for confounders (Column B), this association was attenuated.

When other antidepressants were added to the model, (Column C) the odds ratio for dyspnea when on selective serotonin reuptake inhibitors remained consistent. Although not always significant, all antidepressants were associated with an increased odds of dyspnea at both exams, against our hypothesis.

### *Difference-in-Difference analysis*

**Table 3.9** shows the unadjusted changes in FEV1% from exam 4 to exam 5 in the control and treatment groups. The average FEV1% at exam 4 was similar between the control and treatment groups for all comparisons. In the treatment group that went off selective serotonin reuptake inhibitors (comparison group 1- on/off), the average FEV1% increased from 89% to 93%. The average FEV1% similarly increased in the control group who stayed on selective serotonin reuptake inhibitors (on/on) from 90% to 92%. The net effect (difference-in-difference) of going off selective serotonin reuptake inhibitors was 2% but was not significant ( $p=0.49$ ). Results were similar when adjusting for CES-D score, smoking status, and pack-years.

The average FEV1% decreased from 91% to 89% in the treatment group that went on selective serotonin reuptake inhibitors (comparison group 2-off/on) and increased in the control group who stayed off selective serotonin reuptake inhibitors (off/off) from 94% to 96%. The net effect (difference-in-difference) of going on selective serotonin reuptake inhibitors was 4% and was significant ( $p=0.03$ ). Results were similar when adjusting for CES-D score, smoking status, and pack-years. We also assessed the difference-in-difference analyses for serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants (

**Appendix Table 10** and **Appendix Table 11**); none of these associations were significant.

Results remained consistent when adding an indicator variable for lung function medications to the difference-in-difference models. The control group (those that remained on selective serotonin reuptake inhibitors-on/on) had an FEV1% of 84% at exam 4, which increased to 86% at exam 5 resulting in an absolute difference of 2%. The treatment group (those that went from being on selective serotonin reuptake inhibitors at exam 4 to being off them at exam 5-on/off) had an FEV1% of 81% at exam 4, increasing to 83% at exam 5, with an absolute difference of 2%. The net effect (difference-in-difference) of going off selective serotonin reuptake inhibitors was 0% and was not significant ( $p=0.86$ ). For comparison group 2, when adding lung function medication use to the difference-in-difference models, the control group (those that remained off selective serotonin reuptake inhibitors-off/off) had a FEV1% of 83% at exam 4, which remained consistent at 83% at exam 5 resulting in an absolute difference of 0. The treatment group (those that went on selective serotonin reuptake inhibitors at exam 5-off/on) had an FEV1% of 81% at exam 4, decreasing to 78% at exam 5, with an absolute difference of 3%. The net effect (difference-in-difference) of going on selective serotonin reuptake inhibitors was 3% and was significant ( $p=0.049$ ).

The difference-in-difference in patients reporting dyspnea was then assessed (**Table 3.10**). In the treatment group that went off selective serotonin reuptake inhibitors (on/off), the proportion of patients reporting dyspnea decreased from 27% to 25%. The average proportion of patients reporting dyspnea similarly decreased in the control group who stayed on selective serotonin reuptake inhibitors (on/on) from 25% to 23%. The net effect (difference-in-difference) of going off selective serotonin reuptake inhibitors was 0%. Results were similar when adjusting for CES-D score, smoking status, and pack-years.

The proportion of patients reporting dyspnea increased from 22% to 26% in the treatment group that went on selective serotonin reuptake inhibitors (off/on) and increased in the control group who stayed off selective serotonin reuptake inhibitors (off/off) from 13% to 14%. The net effect (difference-in-difference) of going on selective serotonin reuptake inhibitors was 3%, but was not significant ( $p=0.65$ ).

We also assessed the difference-in-difference analyses for serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants (

**Appendix Table 12 and**

**Appendix Table 13**); none of the analyses were significant but also had small sample sizes for the proportion of patients on treatment.

Similar to FEV1, results remained consistent when adding an indicator variable for lung function medications to the difference-in-difference models for dyspnea. In comparison group 1 the control group decreased from 47% reporting dyspnea at exam 4 to 41% at exam 5, with an absolute difference of 6%. The treatment group increased from 38% at exam 4 to 39% at exam 5, with an absolute difference of 1%. The net effect (difference-in-difference) of going off selective serotonin reuptake inhibitors was 7% and was not significant ( $p=0.44$ ). In comparison group 2, the control group decreased from 29% reporting dyspnea at exam 4 to 24% at exam 5, with an absolute difference of 5%. The treatment group decreased from 33% at exam 4 to 26% at exam 5, with an absolute difference of 7%. The net effect (difference-in-difference) of going off selective serotonin reuptake inhibitors was 2% and was not significant ( $p=0.63$ ).

In summary, adding lung function medications to the models decreased the effect sizes slightly, but the direction and results remained consistent.

#### *Post-hoc analysis*

Since approximately 20% of those on antidepressants still had CES-D scores indicating they were depressed (uncontrolled depression), we looked at the effect CES-D score (both as a continuous measure as dichotomized by cutoffs for depression) had on the crude association. Participants with a CES-D score  $\geq 16$  are identified as having depression, while those with a score  $< 16$  are not [102].

**Appendix Table 14 to 17** compare the crude and adjusted effects. FEV1% at exam 4 and 5 (*Error! Reference source not found. and 15*) showed a small difference when controlling for CES-D as a continuous measure, but the effect is very slight. In the case of dyspnea (*Error! Reference source not found. and 17*) where the effect decreases, it still does not support our hypothesis of depression causing selective serotonin reuptake inhibitors to be poorly associated with FEV1%. The adjusted models still show selective serotonin reuptake inhibitors are inversely associated with FEV1% when controlling for depression symptoms alone.

Results were similar when assessing CES-D dichotomized as cutoffs for depression. None of the analyses resulted in a change in the direction of the relationship between selective serotonin reuptake inhibitors and FEV1% or dyspnea.

## **DISCUSSION**

It is hypothesized that selective serotonin reuptake inhibitors may improve lung function through their anti-inflammatory and serotonergic effects. Prior research on the effects of antidepressants and lung function has been in small studies with minimal confounder control. To fill evidence needs, this study aimed to test the effect of selective serotonin reuptake inhibitors on lung function using a population based cohort with control for confounders. The results did not support our hypothesis; indeed, the associations were in the opposite direction. Using a large population-based prospective dataset, we found that selective serotonin reuptake inhibitors are inversely associated with FEV1%, after controlling for depression score, smoking status, pack-years, and other types of antidepressants. Selective serotonin reuptake inhibitors were associated with a 4.66% decrease in FEV1% at exam 4; after controlling for depression score, smoking status, and pack-years, this association remained significant and in the inverse direction. Furthermore, this association persisted after additionally controlling for serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants. In the adjusted difference-in-difference models, the net effect of going on selective serotonin reuptake inhibitors was 3% for FEV1% ( $p=0.03$ ); those that went on selective serotonin reuptake inhibitors decreased their lung function, while those that remained off increased it. Selective serotonin reuptake inhibitors were also significantly associated with an increased odds of dyspnea at exam 4 and 5. This association was consistently in the positive direction, after including the control variables and other antidepressants in the models. The difference-in-difference analysis also did not support our hypothesis; compared with those who remained off selective serotonin reuptake inhibitors the group that initiated them had a larger increase in the proportion who reported dyspnea, however the point estimate was above the null and had wide confidence intervals.

Both the linear regression and difference-in-difference results were unexpected and in the opposite direction as hypothesized. This association may be by chance, since there were no significant differences

between those who remained on selective serotonin reuptake inhibitors and those who went off. If there were a true harmful effect of selective serotonin reuptake inhibitors and lung function, we would expect to see an improvement in the lung function of those who went off medication compared with the control group. Of note, our sample size was smaller in the on/off groups, which may have prevented us from finding an association. Additionally, we have not come across any previous studies demonstrating patients who went on selective serotonin reuptake inhibitors having a decrease in lung function.

Another hypothesis for this inverse association is depression. Although depression is controlled for through the CES-D score, we have no measure of the severity of depression prior to being on an antidepressant. Additionally, even in individuals who were on antidepressants, the CES-D scores were still elevated and a significant proportion still had CES-D scores  $\geq 16$ , indicating depression. Since depression is linked to increased levels of inflammation [103], it is possible that the increased inflammation seen in depression overrides the potential anti-inflammatory effects of selective serotonin reuptake inhibitors on reducing inflammation. Therefore, what we are really seeing is an increase in inflammation from depression leading to a decrease in lung function rather than the selective serotonin reuptake inhibitors causing a decrease in lung function. Supporting this are results from two randomized, placebo-controlled studies by Brown et al involving patients with asthma and major depressive disorder. The authors found there was no change in the dyspnea scale after treatment with selective serotonin reuptake inhibitors [60, 61]; however, participants who were able to achieve a depression remission had greater reductions in dyspnea than those that did not. Our post-hoc analysis did not support the hypothesis that depression was responsible for the inverse association between selective serotonin reuptake inhibitors and lung function. However, further studies can assess inflammation as a mediator between antidepressant and lung function.

There are several limitations to this study, including several sample-related limitations. We did not assess the specific drug (other than antidepressant type) that was prescribed or the dose. While drugs in an antidepressant class have a similar chemical make-up, other fillers and additives may change their effects on lung function. For example, in the systematic literature review (Chapter 2), it was noted that studies investigating citalopram and fluoxetine were consistently among the studies with positive associations. The dose of the medication would allow us to assess if a certain dosing level is needed for

the anti-inflammatory effects of antidepressants to affect lung function. Additionally, it would be ideal to have a measure of lung function and confounders just prior to taking the antidepressant, and then measure these again after placing participants on the antidepressant. This would allow us to determine the change in confounders (for example depression) in parallel with the change in lung function. Lastly, exam 4 and 5 are separated by approximately 5 years, so our difference-in-difference estimate has a wide gap between estimates.

There are several strengths to this study as well. This investigation was among the first to assess the impact of antidepressants on lung function using epidemiologic methods. Prior studies have been limited to small sample sizes and often did not consider potential confounding; this study included measures of depressive symptoms, smoking status and health insurance. To assess the impact of selective serotonin reuptake inhibitors, we conducted an analysis of individual level data. In order to control for the limitations of this approach, including incomplete confounder control, we additionally performed a difference-in-difference method to estimate the effect of individual-level selective serotonin reuptake inhibitor exposure on lung function. While still potentially suffering from bias due to residual confounding, this method addresses confounding by unmeasured time-invariant attributes.

In conclusion, there is no evidence to support our hypothesis of selective serotonin reuptake inhibitors improving concurrent lung function. Further research can improve upon this study by including measures of confounders prior to and after antidepressant initiation to understand the change in depression symptoms and inflammation.

## TEXT FIGURES & TABLES

Figure 3.1. Timeline of the Multi Ethnic Study of Atherosclerosis and ancillary study exam visits

2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
MESA Exam 1		MESA Exam 2		Exam 3	MESA Exam 4							MESA Exam 5			
					MESA Lung 1							MESA Lung 2			

Table 3.1. Difference-in-difference stratification

	A. SSRI use at Exam 4	B. SSRI use at Exam 5	
<b>Control Group</b>	On	On	Comparison group 1
<b>Treatment Group</b>	On	Off	

	C. SSRI use at Exam 4	D. SSRI use at Exam 5	
<b>Control Group</b>	Off	Off	Comparison group 2
<b>Treatment Group</b>	Off	On	
SSRI-selective serotonin reuptake inhibitor			

Table 3.2. Description of cohort at Exam 4

Sample characteristics	No Antidepressant N=3273		SSRI N=178		SNRI N=42		TCA N=38		Total N=3542	
	N or mean±SD	%	N or mean±SD	%	N or mean±SD	%	N or mean±SD	%	N or mean±SD	%
<b>Age, years, mean±SD</b>	66±10		66±10		64±10		70±10		66±10	
<b>Age group, years</b>										
45-54	445	14	28	16	9	21	3	8	486	14
55-64	1081	33	64	36	13	31	10	26	1172	33
65-74	1026	31	44	25	13	31	13	34	1100	31
75-84	649	20	35	20	7	17	8	21	701	20
>85	72	2	7	4	0	0	4	11	83	2
<b>Gender</b>										
Male	1656	51	65	37	9	21	13	34	1748	49
Female	1617	49	113	64	33	79	25	66	1794	51
<b>Race/ethnicity</b>										
White	1086	33	113	64	30	71	16	42	1254	35
Asian	559	17	4	2	3	7	1	3	567	16
African-American	876	27	19	11	4	10	7	18	907	26
Hispanic	752	23	42	24	5	12	14	36	814	23
<b>Height, cm, mean±SD</b>	166±10		165±9		167±9		164±7		166±10	
<b>BMI, kg/m<sup>2</sup>, mean±SD</b>	28±5		29±6		31±6		29±7		28±5	
<b>Health Insurance</b>										
None	181	6	5	3	2	5	1	3	189	5
Medicaid	268	8	16	9	5	12	7	18	297	8
Medicare	325	10	10	6	3	7	3	8	341	10
HMO	2147	66	128	72	30	71	19	50	2331	66
VA/Other	352	11	19	11	2	5	8	21	384	11
<b>Cigarette smoking status</b>										
Never-smokers	1720	53	80	45	17	42	16	42	1835	52
Former smokers	1257	39	69	39	20	49	17	45	1371	39
Current smokers	286	9	29	16	4	10	5	13	325	9
<b>Smoking history pack-years<sup>#</sup></b>	22±25		27±36		18±15		34±36		22±26	
<b>FEV<sub>1</sub> % predicted, mean±SD</b>	94±18		90±18		91±12		97±16		94±18	
<b>COPD Stage</b>										
None	2551	78	139	78	31	74	29	76	2757	78
Mild	420	13	17	10	6	14	6	16	449	13
Moderate	265	8	19	11	5	12	3	8	295	8
Severe	32	1	2	1	0	0	0	0	35	1
Very Severe	5	.15	1	.60	0	0	0	0	6	.17
<b>Dyspnea</b>	465	14	42	24	14	33	14	37	541	15
<b>CES-D Score, mean±SD</b>	7±7		13±11		11±11		10±8		8±8	
Depressed (CES-D≥16)	413	13	54	30	10	24	8	21	489	14
<b>Corticosteroid use</b>										
Yes	135	4	17	10	2	5	5	13	159	5
No	3138	96	161	91	40	95	33	87	3383	96

SSRI: selective serotonin reuptake inhibitors, TCA: tricyclic antidepressants, SNRI: serotonin-norepinephrine reuptake inhibitors; cm: centimeters; kg: kilogram; m: meter; CES-D: Center for Epidemiological Studies-Depression <sup>#</sup>among ever-smokers. All numbers reported as number and percentage unless otherwise stated. Shaded variables or values were not applicable for mean±SD when reporting percentage.

Table 3.3. Description of cohort at Exam 5

Sample characteristics	No Antidepressant N=2713		SSRI N=152		SNRI N=54		TCA N=25		Total N=2954	
	N or mean±SD	%	N or mean±SD	%	N or mean±SD	%	N or mean±SD	%	N or mean±SD	%
<b>Age, years</b>	69±9		67±9		68±9		70±9		69±9	
<b>Age group, years</b>										
45-54	48	2	4	3	1	2	0	0	53	2
55-64	957	35	66	43	19	35	8	32	1053	36
65-74	871	32	41	27	19	35	9	36	947	32
75-84	693	26	33	22	14	26	5	20	745	25
>85	144	5	8	5	1	2	3	12	156	5
<b>Gender</b>										
Male	1367	50	53	35	15	27	12	48	1449	49
Female	1346	50	99	65	41	73	13	52	1505	51
<b>Race/ethnicity</b>										
White	983	36	93	61	39	72	11	44	1134	38
Asian	414	15	7	5	3	6	0	0	424	14
African-American	723	27	26	17	6	11	7	28	763	26
Hispanic	593	22	26	17	6	11	7	28	633	21
<b>Height, cm</b>	166±10		164±10		166±8		165±9		166±10	
<b>BMI, kg/m<sup>2</sup></b>	28±5		29±6		31±6		27±5		28±6	
<b>Health Insurance</b>										
None	130	5	5	3	1	2	0	0	136	5
Medicaid	218	8	8	5	4	7	2	8	233	8
Medicare	298	11	16	11	3	6	3	12	320	11
HMO	1777	66	100	66	42	78	17	38	1944	66
VA/Other	287	11	23	15	4	7	3	12	318	11
<b>Cigarette smoking status</b>										
Never-smokers	1490	55	68	45	25	48	6	24	1595	54
Former smokers	1034	38	70	46	25	48	13	52	1146	39
Current smokers	170	6	13	9	2	4	6	24	191	7
<b>Smoking history pack-years<sup>#</sup></b>	18±24		25±34		23±26		31±30		22±25	
<b>FEV<sub>1</sub> % predicted, mean (SD)</b>	96±20		93±20		91±16		86±20		95±20	
<b>COPD Stage</b>										
None	1997	74	109	72	44	79	13	52	2169	74
Mild	425	16	23	15	3	5	6	24	457	16
Moderate	242	9	17	11	9	16	5	20	275	9
Severe	43	2	3	2	0	0	1	4	47	2
Very Severe	3	0.11	0	0	0	0	0	0	3	.10
<b>Dyspnea, No. (%)</b>	385	14	35	23	13	24	5	20	440	15
<b>CES-D Score</b>	8±7		12±10		12±10		9±8		8±8	
Depressed (CES-D≥16)	353	13	47	31	14	26	5	20	421	14
<b>Corticosteroid use</b>										
Yes	232	9	27	18	10	19	7	28	279	9
No	2481	92	125	82	44	82	18	72	2675	91
<b>Time between exam ¼ and 5 spirometry in days</b>	1890±279		1885±263		1860±273		1863±263		1889±278	

SSRI: selective serotonin reuptake inhibitors, TCA: tricyclic antidepressants, SNRI: serotonin-norepinephrine reuptake inhibitors; cm: centimeters; kg: kilogram; m: meter; CES-D: Center for Epidemiological Studies-Depression <sup>#</sup>among ever-smokers. All numbers reported as number and percentage unless otherwise stated. Shaded variables or values were not applicable for mean±SD when reporting percentage.

Table 3.4. Associations of confounders with selective serotonin reuptake inhibitors and outcome variables:  
Exam 4

Sample characteristics	Crude relationship to					
	OR	A. SSRI 95% CI	b	B. FEV1% 95% CI	OR	C. Dyspnea 95% CI
<b>Health Insurance</b>						
None	Ref	Ref	Ref	Ref	Ref	Ref
Medicaid	<b>2.23</b>	<b>0.81 to 6.16</b>	1.07	-2.22 to 4.35	1.46	0.87 to 2.44
Medicare	<b>1.11</b>	<b>0.37 to 3.30</b>	-0.82	-4.02 to 2.38	1.32	0.79 to 2.19
HMO	<b>2.24</b>	<b>0.91 to 5.55</b>	0.09	-2.59 to 2.76	<b>1.11</b>	<b>0.72 to 1.72</b>
VA/Other	<b>2.24</b>	<b>0.83 to 6.00</b>	2.54	-0.60 to 5.68	1.39	0.82 to 2.28
<b>Cigarette smoking status</b>						
Never-smokers	Ref	Ref	Ref	Ref	Ref	Ref
Former smokers	1.29	0.94 to 1.78	<b>-4.04</b>	<b>-5.28 to -2.79</b>	1.23	1.01 to 1.50
Current smokers	<b>2.20</b>	<b>1.42 to 3.41</b>	<b>-9.68</b>	<b>-11.78 to -7.58</b>	<b>1.56</b>	<b>1.15 to 2.11</b>
Smoking pack-years*	<b>1.09</b>	<b>1.03 to 1.15</b>	<b>-1.77</b>	<b>-2.05 to -1.50</b>	<b>1.08</b>	<b>1.04 to 1.12</b>
<b>CES-D Score</b>	<b>1.06</b>	<b>1.05 to 1.08</b>	<b>-0.09</b>	<b>-0.17 to -0.02</b>	<b>1.07</b>	<b>1.06 to 1.08</b>

Bold indicates p<0.20 \*Smoking pack-years is per 10-years

Table 3.5. Percent of predicted forced expiratory volume in one second at exam 4: unadjusted and adjusted models

	A. Unadjusted model		B. Adjusted model 1		C. Adjusted model 2	
	b	95% CI	b	95% CI	b	95% CI
<b>SSRI</b>	<b>-4.66</b>	<b>-7.31 to -2.02</b>	<b>-3.18</b>	<b>-5.80 to -0.56</b>	<b>-3.30</b>	<b>-5.92 to -0.67</b>
<b>SNRI</b>					-4.43	-9.73 to 0.86
<b>TCA</b>					2.12	-2.91 to 7.15
<b>Cigarette smoking status</b>						
<b>Never-smokers</b>			Ref	Ref	Ref	Ref
<b>Former smokers</b>			-1.02	-2.41 to 0.37	-0.99	-2.38 to 0.40
<b>Current smokers</b>			<b>-5.33</b>	<b>-7.59 to -3.06</b>	<b>-5.31</b>	<b>-7.57 to -3.05</b>
<b>Smoking pack-years</b>			<b>-0.15</b>	<b>-0.18 to -0.12</b>	<b>-0.15</b>	<b>-0.18 to -0.12</b>
<b>CES-D Score</b>			-0.06	-0.14 to 0.02	-0.06	-0.14 to 0.02

Bold indicates significant ( $p < 0.05$ ). Shaded variables or values were not included in the model.

Beta shows the mean difference.

Table 3.6. Percent of predicted forced expiratory volume in one second at exam 5: unadjusted and adjusted models

	A. Unadjusted model		B. Adjusted model 1		C. Adjusted model 2	
	b	95% CI	b	95% CI	b	95% CI
<b>SSRI</b>	<b>-3.22</b>	<b>-6.37 to -0.08</b>	-2.43	-5.56 to 0.70	-2.25	-5.39 to 0.90
<b>SNRI</b>					-4.26	-9.53 to 1.01
<b>TCA</b>					-5.96	-12.70 to 0.79
<b>Cigarette smoking status</b>			Ref	Ref	Ref	Ref
<b>Never-smokers</b>			-0.22	-1.92 to 1.49	-0.17	-1.87 to 1.54
<b>Former smokers</b>			<b>-6.25</b>	<b>-9.46 to -3.04</b>	<b>-6.17</b>	<b>-9.38 to -2.96</b>
<b>Current smokers</b>						
<b>Smoking pack-years</b>			<b>-0.14</b>	<b>-0.18 to -0.10</b>	<b>-0.14</b>	<b>-0.18 to -0.10</b>
<b>CES-D Score</b>			-0.07	-0.17 to 0.02	-0.07	-0.16 to 0.03

Bold indicates significant ( $p < 0.05$ ). Shaded variables or values were not included in the model.

Beta shows the mean difference.

Table 3.7. Dyspnea at exam 4: unadjusted and adjusted models

	A. Unadjusted model		B. Adjusted model 1		C. Adjusted model 2	
	OR	95% CI	OR	95% CI	OR	95% CI
<b>SSRI</b>	1.99	1.41 to 2.80	1.32	0.91 to 1.91	1.27	0.88 to 1.85
<b>SNRI</b>					1.98	0.98 to 4.00
<b>TCA</b>					3.27	1.78 to 6.01
<b>Cigarette smoking status</b>			Ref	Ref	Ref	Ref
<b>Never-smokers</b>						
<b>Former smokers</b>			1.06	0.85 to 1.34	1.05	0.84 to 1.32
<b>Current smokers</b>			1.14	0.81 to 1.61	1.13	0.80 to 1.60
<b>Smoking pack-years</b>			1.01	1.00 to 1.01	1.01	1.00 to 1.01
<b>CES-D Score</b>			1.07	1.06 to 1.08	1.07	1.06 to 1.08

Shaded variables or values were not included in the model.

Table 3.8. Dyspnea at exam 5: unadjusted and adjusted models

	<b>A. Unadjusted model</b>		<b>B. Adjusted model 1</b>		<b>C. Adjusted model 2</b>	
	<b>OR</b>	<b>95% CI</b>	<b>OR</b>	<b>95% CI</b>	<b>OR</b>	<b>95% CI</b>
<b>SSRI</b>	1.76	1.20 to 2.57	1.35	0.90 to 2.01	1.35	0.91 to 2.02
<b>SNRI</b>					1.52	0.79 to 2.92
<b>TCA</b>					1.07	0.43 to 2.66
<b>Cigarette smoking status</b>						
<b>Never-smokers</b>			Ref	Ref	Ref	Ref
<b>Former smokers</b>			1.03	0.81 to 1.32	1.03	0.80 to 1.32
<b>Current smokers</b>			0.88	0.56 to 1.38	0.88	0.56 to 1.39
<b>Smoking pack-years</b>			1.01	1.01 to 1.02	1.01	1.01 to 1.02
<b>CES-D Score</b>			1.06	1.04 to 1.07	1.06	1.04 to 1.07

Shaded variables or values were not included in the model.

Table 3.9. Unadjusted and adjusted difference-in-difference analysis of percent of predicted forced expiratory volume in one second: selective serotonin reuptake inhibitors

<b>Unadjusted</b>				
<b>Comparison group 1 n=125</b>	<b>SSRI use at Exam 4</b>	<b>SSRI use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	90%	92%	2	
Treatment Group (on/off)	89%	93%	4	
Difference	1	1	2	0.49
<b>Comparison group 2 n=2285</b>				
Control Group (off/off)	94%	96%	2	
Treatment Group (off/on)	91%	89%	2	
Difference	3	7	4	0.03
<b>Adjusted<sup>†</sup></b>				
<b>Comparison group 1 n=125</b>	<b>SSRI use at Exam 4</b>	<b>SSRI use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	93%	94%	1	
Treatment Group (on/off)	91%	93%	2	
Difference	2	1	1	0.93
<b>Comparison group 2 n=2285</b>				
Control Group (off/off)	93%	94%	1	
Treatment Group (off/on)	89%	87%	2	
Difference	4	7	3	0.04

The first comparison group had 71 patients that remained on selective serotonin reuptake inhibitors (control group) compared to 54 who went from being on selective serotonin reuptake inhibitors at exam 4 to being off them at exam 5 (treatment group). The second comparison group had 2225 patients that remained off selective serotonin reuptake inhibitors (control group) compared to 60 who went on them at exam 5 (treatment group).

<sup>†</sup>Adjusted for Centers for Epidemiologic Studies Depression Score, smoking status (never, former current) and smoking pack-years.

Table 3.10. Unadjusted and adjusted difference-in-difference analysis of proportion of participants reporting dyspnea: selective serotonin reuptake inhibitors

<b>Unadjusted</b>				
<b>Comparison group 1 n=131</b>	<b>SSRI use at Exam 4</b>	<b>SSRI use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	25%	23%	2%	
Treatment Group (on/off)	27%	25%	2%	
Difference	2	2	0	0.88
<b>Comparison group 2 n=2279</b>				
Control Group (off/off)	13%	14%	1%	
Treatment Group (off/on)	22%	26%	4%	
Difference	9	12	3	0.65
<b>Adjusted<sup>†</sup></b>				
<b>Comparison group 1 n=131</b>	<b>SSRI use at Exam 4</b>	<b>SSRI use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	26%	23%	1%	
Treatment Group (on/off)	27%	24%	3%	
Difference	1	1	2	0.93
<b>Comparison group 2 n=2279</b>				
Control Group (off/off)	13%	14%	1%	
Treatment Group (off/on)	16%	19%	3%	
Difference	3	5	2	0.60

The first comparison group had 71 patients that remained on selective serotonin reuptake inhibitors (control group) compared to 54 who went from being on selective serotonin reuptake inhibitors at exam 4 to being off them at exam 5 (treatment group). The second comparison group had 2225 patients that remained off selective serotonin reuptake inhibitors (control group) compared to 60 who went on them at exam 5 (treatment group).

<sup>†</sup>Adjusted for Centers for Epidemiologic Studies Depression Score, smoking status (never, former current) and smoking pack-years.

## CHAPTER 4. A LARGE COHORT STUDY ON THE ASSOCIATION BETWEEN SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND THE SEVERITY OF PULMONARY DISEASE

### ABSTRACT

*Background:* Chronic Obstructive Pulmonary Disease (COPD) refers to a group of lung diseases that cause airflow obstruction, respiratory muscle weakness, and reduced lung function that result in breathing-related problems (such as increased breathlessness, frequent coughing, and tightness in the chest). COPD is characterized by periodic episodes of increased symptoms (e.g., shortness of breath, irregular breathing, and worse coughing with increased phlegm production), also called pulmonary exacerbations. Although pulmonary exacerbations are expected in COPD, epidemiological studies in the general population and in primary care practices show that pulmonary exacerbations can even occur among those who do not meet criteria for COPD. Due to their anti-inflammatory and serotonergic effects, selective serotonin reuptake inhibitors may provide a lung function and exacerbation-prevention benefit. *Objectives:* This study aims to investigate whether those on selective serotonin reuptake inhibitors have a lower pulmonary exacerbation rate than those not on selective serotonin reuptake inhibitors. We will also assess if inflammatory markers mediate the association between selective serotonin reuptake inhibitors and lung function. *Methods:* The data for this paper came from the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS). At each annual visit, information was collected on medical history and current medications, including antidepressants. Pulmonary exacerbation history was gathered prospectively (every 3 months) with the use of a structured questionnaire. Cox proportional hazards models with time-dependent covariates were used to obtain hazard ratios (HRs) for time to first exacerbation since enrolling in the study. *Main results:* There were 2221 eligible participants after exclusions for missing data. Findings indicate an increased rate of exacerbations for those on selective serotonin reuptake inhibitors compared with those not on selective serotonin reuptake inhibitors, against our hypothesis. In the crude analysis, for any given visit, if a participant was on selective serotonin reuptake inhibitors the rate of first exacerbation was 36%

higher (crude HR 1.36, 95% CI: 1.13 to 1.65) than if they were not on selective serotonin reuptake inhibitors; this association decreased and was no longer significant after adjustment (adjusted HR: 1.12, 95% CI: 0.86 to 1.44). Inflammation was not a mediator in the association between selective serotonin reuptake inhibitors and FEV1. *Conclusions:* We found no evidence to support the hypothesis that selective serotonin reuptake inhibitors provide a benefit in reducing pulmonary exacerbations. Additionally, there was no evidence to support the hypothesis that inflammation is a mediator in the association between selective serotonin reuptake inhibitors and lung function.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by periodic episodes of worsening symptoms (e.g., shortness of breath, irregular breathing, and worse coughing with increased phlegm production), also called pulmonary exacerbations [104, 105]. Exacerbations in COPD are important because they have a negative impact on quality of life, increase mortality rates, accelerate the decline in lung function, and have high societal costs. Although exacerbations are expected in COPD, epidemiological studies in the general population [106-108] and in primary care practices [109] show that exacerbation-like events (exacerbations similar to COPD) can occur among those who do not meet criteria for COPD [110]. Tan and colleagues looked at cross-sectional data of 5,176 people from a population-based study on lung health. Participants were queried on chronic respiratory symptoms (chronic cough or phlegm, wheezing and shortness of breath) and exacerbations. The study defined an exacerbation as 'a period of worsening of breathing problems that got so bad that it interfered with usual daily activities or caused the individual to miss work'. The authors found that individuals without diagnosed COPD or asthma have exacerbation-like events although at a lower frequency compared with those with COPD.

Inflammation is responsible for many of the symptoms and reduction in quality of life [13] in COPD and is especially pronounced during exacerbations. Inflammatory cells damage lung parenchyma, leading to a reduced ability of the airways to remain open. Even in individuals with mild COPD [2], inflammation reduces lung function, accelerates decline in lung function overtime, and increases the risk for exacerbations [3-7]. Furthermore, in young adults without COPD, and independent of asthma, smoking, and body weight, an inverse association is seen between lung volumes and inflammation [83]. Since inflammation is inversely associated with lung volumes and quality of life in individuals with and without COPD, reducing inflammation may be beneficial for those with low lung function but no diagnosed disease, in addition to those with clinically defined obstructive disease.

Agents that reduce inflammation are hypothesized to result in improvements in lung function and exacerbation frequency. Providing support for this hypothesis, current therapies for increasing lung function, such as inhaled corticosteroids, act in part by reducing inflammation. However, inhaled

corticosteroids do not entirely inhibit inflammation [14, 15] and have significant side effects at higher doses. This lack of fully effective therapy and poor side effect profile lead researchers to search for better options. In the pursuit of alternative medications, selective serotonin reuptake inhibitors are considered. In addition to having anti-inflammatory properties, they act upon serotonin, which is integral in central breathing control [17]. The combination of their anti-inflammatory and serotonergic effects may provide users of selective serotonin reuptake inhibitors with a lung function and exacerbation-prevention benefit while avoiding the side effects of inhaled steroids.

### *Mediation*

A decreased forced expiratory volume in one second (FEV1) is the measure primarily used to show reduced lung function in COPD [51]. The association between selective serotonin reuptake inhibitors and lung function was explored in Chapter 3, however one area largely untested is inflammatory markers being the mechanism behind the presumed association between selective serotonin reuptake inhibitors and lung function. Reduced lung function is associated with increased levels of the inflammatory markers interleukin-6 (IL-6) and C-reactive protein (CRP) [111]. Selective serotonin reuptake inhibitors reduce these inflammatory cytokines, although results have varied and are typically measured in participants with major depressive disorder, not COPD [41].

Seen in both animal [32-34], and human [16] models, selective serotonin reuptake inhibitors reduce the microglial production of the PI-cytokine TNF- $\alpha$  and the free radical nitric oxide, both key players in inflammation in the brain [35]. In the lungs, fluoxetine, a selective serotonin reuptake inhibitor, inhibits airway inflammation through affecting the capacity of monocytes and lung epithelial cells to produce inflammatory cytokines [36]. These effects are potentially due to selective serotonin reuptake inhibitors' influence on serotonin, as serotonin has a role in anti-inflammatory processes [33, 37].

Although tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors are all thought to have serotonergic effects, in two similar studies by Bianchi, only selective serotonin reuptake inhibitors have an anti-inflammatory effect through increasing the level of

serotonin [33, 37]. Additional trials show serotonin-norepinephrine reuptake inhibitors [16] and tricyclic antidepressants [38] do not have anti-inflammatory effects.

The selective influences of serotonin may explain the discrepancy between the effects of selective serotonin reuptake inhibitors and other classes of antidepressants on inflammation. Both tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors increase norepinephrine, but selective serotonin reuptake inhibitors do not [39]. Consistent with the known pro-inflammatory effects of norepinephrine on innate immune cells [40], serotonin-norepinephrine reuptake inhibitors are associated with an *increase* in inflammatory markers [41], indicating that norepinephrine may cancel out the anti-inflammatory effects of serotonin.

## PURPOSE

We therefore aim to investigate whether those who use selective serotonin reuptake inhibitors have a lower exacerbation rate than those who do not use selective serotonin reuptake inhibitors. This study tests whether selective serotonin reuptake inhibitor use is associated with a reduction in pulmonary exacerbations, after adjusting for potential confounders, in a large cohort of both individuals with and without COPD. Additionally, we assess if inflammatory markers mediate the association between selective serotonin reuptake inhibitor use and lung function (specifically, FEV1).

## METHODS

The data for this paper came from the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), funded by the National Heart, Lung and Blood Institute (ClinicalTrials.gov Identifier: NCT01969344). SPIROMICS is an observational study that prospectively collected phenotypic, biomarker, genetic, genomic, and clinical data from subjects with the purpose of identifying homogeneous subgroups of COPD patients as well as preliminary validation of intermediate biological or clinical outcome measures. Over 2700 participants were enrolled between November 12, 2010 and July 31, 2015 at six clinical centers (Winston-Salem, NC; Ann Arbor, MI; San Francisco, CA; Los Angeles, CA; New York City, NY; and Salt Lake City, UT). As seen in **Figure 4.1**, there are baseline (visit 1) and three annual in person

follow-up visits (visits 2-4); additionally, participants receive quarterly telephone calls in between visits to assess for exacerbations, hospitalizations, and mortality.

The SPIROMICS protocol, including information about the populations from which recruitment occurred, detailed criteria, and other information, is available at [www.csc.unc.edu/spiromics](http://www.csc.unc.edu/spiromics). As shown in **Table 4.1**, four strata were enrolled, two with and two without COPD: non-smokers, smokers, mild/moderate COPD and severe COPD. Briefly, participants were between 40-80 years of age at baseline who either had a smoking history of  $\leq 1$  pack-year (considered a non-smoker) and no known current lung disease (no history of COPD) (n=202) or current or former smokers ( $>20$  pack-years) with and without evidence of COPD (smokers without COPD (n=941), mild/moderate COPD (n=1207), and severe COPD (n=624)). Exclusion criteria are non-COPD obstructive lung disease or a history of diseases or treatments likely to interfere with interpretation of study tests, BMI  $> 40$  kg/m<sup>2</sup> at baseline, hypersensitivity or intolerance of bronchodilators used in assessments, and diagnosis of unstable cardiovascular disease [112]. Full inclusion/exclusion criteria for each strata are given in **Appendix Table 18**.

Participants were recruited by means of physician referral, advertisement for the study in clinical areas or self-referral at the study website ([www.spiromics.com](http://www.spiromics.com)). The institutional review boards of all collaborating institutions and the National Heart Lung and Blood Institute (National Institutes of Health, Bethesda, MD, USA) approved the protocols of SPIROMICS and all procedures described herein. All participants provided informed consent. SPIROMICS approved a proposal for this analysis.

## MEASURES

### *Exposure variable*

The exposure is use of selective serotonin reuptake inhibitors. At each annual visit, information was collected on medical history and current medication use. Information on medications and supplements used in the past 3 months were collected through a structured questionnaire. The questionnaire asked detailed information on common oral and inhaled corticosteroids, bronchodilators, statins, beta-blockers, and antioxidants; in addition, participants were asked to list all medications taken in the previous 3 months. The

use of different antidepressants was classified according to the Anatomical Therapeutic Chemical classification (selective serotonin reuptake inhibitors, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors) [85]. We coded this variable into an indicator variable (yes (1)/no (0)) for each antidepressant class to indicate whether a participant was taking the drug or not at the time of the visit.

#### *Outcome variable*

Self-reported exacerbation data was gathered prospectively by quarterly phone calls and annual visits with the use of a structured questionnaire. Participants were asked how many episodes of chest trouble flare ups have they had since the last follow-up ('since your last (clinic visit or telephone contact) on (date), have you had a flare-up of your chest trouble?'; 'If Yes, how many episodes of chest trouble flare ups have you had since (date)?'). If an episode was reported, further questions on antibiotics, oral steroids, and office visits, and hospitalizations were queried. Acute exacerbations were defined as events that required health care (i.e., office visit, hospital admission, or emergency department visit for a respiratory flare-up) involving the use of antibiotics or systemic corticosteroids, or both. The participants' usual providers, who were aware of their patient's enrollment in an observational study, managed exacerbations; the study did not provide guidance on management.

#### *Hypothesized confounders*

To identify potential confounders and the minimal set necessary for control, we developed a directed acyclic graph based on previous literature (**Appendix Figure 2**). From the literature aided by the directed acyclic graph, we deemed age, gender, depressive symptoms, baseline FEV1, and number of prior exacerbations before enrolling in the study to be potential confounders.

Age: Increased age is associated with increased exacerbations [113, 114] and increased likelihood of antidepressant use (after the age of 12) [115]. We used age as a continuous variable.

Gender: Women are twice as likely as men to take antidepressant medication [115]. Men have an increased risk for exacerbations [116]. Site personnel determined the gender of the participants, i.e. the participants

did not report it. For those who were genotyped, genotyping sex was compared with the response on the form and there was complete agreement. Gender is coded dichotomously (male (0)/female (1)).

Smoking status and pack-years: Increased smoking is associated with an increased risk for exacerbations [117] and depression is associated with higher smoking rates, thereby increasing exacerbations. Depression is also associated with antidepressant use. Smoking status is categorized into current smokers or former smokers (1), defined as >20 pack-years, and never smokers (0), defined as ≤1 pack-year.

Pack-years is a measure of smoking status for duration and amount of smoking. Quantification of pack-years is important because increased tobacco exposure is closely associated with increased exacerbations [93, 94]. Additionally, increased pack-years are seen in depression [95]. Pack-years will be used as a continuous variable.

Depressive symptoms: Current depressive symptoms are associated with increased risk for exacerbations [105, 118] and with antidepressant use. Although the argument can be made that depressive symptoms is on the causal pathway between selective serotonin reuptake inhibitors and FEV1, we were more concerned with potential confounding as this is not the causal pathway of interest in this study. In SPIROMICS, the Hospital Anxiety and Depression Scale (HADS) score is used at each annual visit to assess for depressive symptoms. This 7-item questionnaire assesses enjoyment, cheerfulness, lethargy, and self-confidence.

Although baseline FEV1 and number of prior exacerbations are not part of the minimal sufficient adjustment sets for estimating the total effect of selective serotonin reuptake inhibitors on exacerbations, we will include them in the model since they are strongly indicative of risk for exacerbations.

Baseline FEV1: A decreased forced expiratory volume in one second (FEV1) is the measure primarily used to show reduced lung function in COPD [51]. Predicted reference values have been calculated and compared with samples of healthy subjects drawn from the general population to yield percent predicted (%) standards. While many different percent predicted standards exist, the American Thoracic Society uses an equation that gives referents based on height, age, gender, and race [86]. A lower FEV1 is associated with an increased risk of exacerbations [114, 118, 119] and is a measure of disease severity. FEV1 was measured in SPIROMICS on a rolling sealed spirometer using the 2005 ATS/ERS guidelines for pulmonary

function testing and interpretation [50, 120, 121]. In order to include a baseline measure of severity of disease, continuous percent of predicted FEV1 at visit 1 (baseline) will be used.

Number of prior exacerbations before enrolling in the study: Prior exacerbations are a strong indication of future risk for exacerbations [119]. This information was gathered at the baseline visit through a structured questionnaire. Participants were asked if they had an episode of breathing problems in the last 12 months and if yes to provide how many episodes. For each episode, they were then asked further questions on additional antibiotic use, oral steroids, health care, hospital and emergency room visits.

#### *Inflammation as a potential mediator*

Part of the hypothesis for selective serotonin reuptake inhibitors' therapeutic effect on lung function is through a reduction in inflammation. Inflammatory markers include serum levels of IL-6 and CRP, measured at visits 1 and 2 in the morning after a fast. Approximately 70 ml of blood was collected per visit, including plasma and serum.

## **ANALYTIC APPROACH**

Analyses were conducted in SAS 9.4. We excluded participants if a) they did not have exposure (medication) information available b) were on more than one antidepressant at the same time or c) were missing data on any confounder included in the model. For more details on decision about missing data, see *Error! Reference source not found.*, **Handling Missing Data**.

Confounder selection: After identifying a set of potential confounders, we explored which of the added covariates had the most influence on the parameter of interest. We then added a minimally adjusted model that included only the covariates that changed the crude exposure-outcome hazard ratio (HR) by more than 10%. Since prior literature shows strong relationships between these hypothesized confounders and both selective serotonin reuptake inhibitors and exacerbations, we also created a fully adjusted model using all hypothesized confounders.

Main analyses: Time to first exacerbation was calculated. Observation time began on the day the subject enrolled into the study. If any participants were lost to follow-up or died, they were censored at the date of last known contact.

#### *Time to first exacerbation*

A Cox proportional hazards model with time-dependent covariates (sometimes called an extended cox model) [122] was used to obtain hazard ratios (HRs) for time to first exacerbation since enrolling in the study [123]. Time dependent variables included smoking status, smoking pack-years, depression score, and antidepressant use [124]. Fixed covariates included age at baseline, gender, baseline FEV1 and number of exacerbations prior to enrolling in the study. The proportional hazards assumptions was checked to determine if there was a constant relationship between the outcome and the covariate, see *Error! Reference source not found., Assessing proportional hazards* for details on checking the modeling assumptions. Results are presented as HRs with 95% confidence intervals (CI).

#### *Mediation*

Data from visit 1 and visit 2 (when both spirometry (FEV1) and inflammatory markers were evaluated) are used to test the hypothesis that the effect of selective serotonin reuptake inhibitors on lung function is partly mediated through a reduction in inflammation. Mediation was assessed using the four Baron and Kenny steps: 1) the direct relationship between the dependent variable (FEV1) and the independent variable (selective serotonin reuptake inhibitors) was meaningful, 2) the independent variable (selective serotonin reuptake inhibitors) was associated with the mediator (inflammation), 3) the mediator was associated with the dependent variable and 4) a previously meaningful relationship between the independent and dependent variable was reduced in magnitude after controlling for the mediator (assumptions were checked: controlled for mediator outcome confounding and there was no interaction between the exposure and mediator) [125].

## **RESULTS**

### *Sample characteristics*

As seen in **Table 4.2**, 81% of the SPIROMICS cohort was eligible for this study (2221 eligible participants). The mean age of the sample at the start of the study was 64 years; 48% were women, the average height was 170 cm with an average weight of 81 kg. The cohort consisted of 79% White, 16% Black, 1% Asian, 2% Pacific Islander and less than 1% each consisting of American Indian and mixed race/ethnicity. Approximately 34% were smokers, with an average of 48 pack-years. The mean percent predicted FEV1 was 67%. The average HADS score was four, with 18% of the cohort classified as being depressed. Participants had an average of 0.4 (range 0-6) exacerbations prior to enrolling in the study. Twelve individuals were on more than one antidepressant at any point during follow-up and therefore excluded from further analyses.

**Appendix Table 19** compares the baseline characteristics between the antidepressant groups. Notably, the no antidepressant group had a higher proportion of men and black participants and a lower HADS score.

### *Confounders*

Only HADS depression score changed the crude HR by 10% or more, as seen in **Table 4.3**. As mentioned previously, prior literature shows strong relationships between the hypothesized confounders and both selective serotonin reuptake inhibitors and exacerbations, so we have decided to keep them in an additional fully adjusted model.

### *Time dependent Cox regression*

There were 837 (38%) participants who reported having an exacerbation during follow-up; 144 (17%) of these were users of selective serotonin reuptake inhibitors. The average follow-up time was 864±301 (range 75 to 1889) days; the time to first reported exacerbation since enrolling in the study was 433±328 (range: 63 to 1921) days. Results for the time-dependent Cox regression are reported in

**Table 4.4.** In the crude analysis, for any given visit, if a participant was on selective serotonin reuptake inhibitors they had a 36% higher rate of first exacerbations (crude HR 1.36, 95% CI: 1.13 to 1.65) than if they were not on selective serotonin reuptake inhibitors. This association decreased and was no longer significant after adjustment (adjusted HR: 1.12, 95% CI: 0.86 to 1.44). This was true when adjusting for HADS depression score alone (adjusted model 1) or the complete adjusted model (adjusted model 2). When including only participants with COPD (**Table 4.5**), there was a significant association in the crude and depression adjusted model, but the confidence intervals widened slightly in the fully adjusted model.

As seen in

**Appendix Table 20** and **Appendix Table 21**, there were no significant associations between serotonin norepinephrine reuptake inhibitors or tricyclic antidepressants and exacerbations. As shown in **Appendix Table 22**, in any given exam, if a participant was on antidepressants, their rate of first exacerbation is 38% higher (crude HR: 1.38, 95% CI: 1.56 to 1.64) than if they were not on any antidepressant; but this also was no longer meaningful after adjustment.

#### *Post-hoc analyses*

Similar to Chapter 3, approximately 30% of those on antidepressants still had HADS scores indicating they were depressed (uncontrolled depression); therefore, we stratified by HADS scores indicating depression to see if there was potential for confounding that was not sufficiently controlled. Participants with a HADS score  $\geq 8$  are identified as having depression, while those with a score  $< 8$  are not [126]. At baseline, there were 389 participants identified as having depression (average HADS:  $10 \pm 2$ ) and 1820 without depression (average HADS:  $3 \pm 2$ ). There were 89 (23%) participants that were depressed and on selective serotonin reuptake inhibitors and 223 (12%) that were not depressed and on selective serotonin reuptake inhibitors. The results of the crude and adjusted cox models, stratified by depression status, are presented in **Appendix Table 23** and **Appendix Table 24**. There was still no evidence to support our hypothesis of a protective effect from selective serotonin reuptake inhibitors.

#### *Mediation*

Inflammatory markers included CRP and IL-6. There were 1,346 participants who had inflammatory markers and pulmonary function measured at visit 1 and 390 who had them measured at visit 2. Selective serotonin reuptake inhibitors were not found to have a beneficial effect on FEV1 (**Tables 4.6 & 4.7, Column A**), however performing a mediational analysis will still allow us investigate why our hypothesis did not hold. The inflammatory markers were tested for their association between selective serotonin reuptake inhibitors and FEV1. Higher IL-6 measures were associated with a lower likelihood of being on selective serotonin reuptake inhibitors only at visit 2 (

**Table 4.6, Column B**). At neither time point was there a meaningful association between CRP and selective serotonin reuptake inhibitors (**Table 4.7, Column B**). Higher CRP measures were associated with lower FEV1 (**Table 4.7, Column C**), but this was not true in IL-6 (

**Table 4.6, Column C).** After controlling for inflammatory cytokines, the effect of selective serotonin reuptake inhibitors on FEV1 remained approximately the same, both at visit 1 and 2 (

**Table 4.6 and Table 4.7, Column D).** Neither IL-6 nor CRP were associated with both the exposure and outcome measures.

Since there was no association between IL-6 and FEV1, but it has previously been associated in prior studies of COPD patients [127, 128], we performed an additional mediational analysis, excluding those without COPD (n=369 at visit 1 and n=108 at visit 2) to see if the association was seen in those with lower lung function. However, our results did not change (**Appendix Table 25** and

*Appendix Table 26).*

In summary, neither IL-6 nor CRP were found to have a consistent relationship with both selective serotonin reuptake inhibitors and only CRP was found to be related to FEV1.

## **DISCUSSION**

We hypothesized that participants on selective serotonin reuptake inhibitors would be associated a lower exacerbation rate than those not on selective serotonin reuptake inhibitors. We are unaware of any studies that have investigated this association. This study aimed to test the association between selective serotonin reuptake inhibitors and exacerbations in a cohort of adults with and without COPD with appropriate confounder control. The results did not support our hypothesis; indeed, associations were in the opposite direction. Using a large dataset, we found that selective serotonin reuptake inhibitors were associated with a 36% higher rate of first exacerbation since enrolling in the study compared with not being on a selective serotonin reuptake inhibitor. After controlling for age, gender, current smoking status, pack-years, baseline FEV1, HADS depression score and number of exacerbations prior to enrolling in the study these associations were no longer significant but remained in the same direction. Results remained similar when stratifying by depression status. There was no association between selective serotonin reuptake inhibitors and rate of first exacerbation in depressed participants.

We also examined the potential mediational role of inflammatory markers between selective serotonin reuptake inhibitors and lung function. We were surprised to find that IL-6 was not associated with FEV1 in the mediation analysis, since prior research has associated IL-6 with FEV1 [127, 128]. This persisted even when removing participants without COPD.

As a secondary analysis, we looked at other antidepressant groups. No association was seen in the serotonin norepinephrine reuptake inhibitors and tricyclic antidepressant groups.

There are several limitations to this study, including several sample-related limitations. Unfortunately, we do not have data on the specific drug (other than antidepressant type) that was prescribed or the dose. While drugs in an antidepressant class have a similar chemical make-up, other fillers and

additives may change their effects on lung function. For example, in the systematic literature review (Chapter 2), it was noted that studies investigating citalopram and fluoxetine were consistently among the studies with positive associations. The dose of the medication would allow us to assess if a certain dosing level is needed for the anti-inflammatory effects of antidepressants to affect lung function. Additionally, we would ideally like our mediational analysis to have longitudinal data (with the visits are separated by a maximum of a few months) where our independent variable preceded the mediational variable and the mediational variable precedes the dependent variable in order to establish temporality. However, in these data the independent variable (selective serotonin reuptake inhibitors) and the mediational variable (inflammatory markers) were taken at the same exam. If we were to use the longitudinal data, our sample sizes would be severely diminished, since there was a large drop in the number of participants who had blood draws at visit 2. Additionally, the timing of the measurement is spaced out by a year or more, which is unlikely to be relevant as we hypothesize a concurrent effect.

There are several strengths to this study as well. This investigation was among the first to assess the impact of antidepressants on pulmonary exacerbations using epidemiologic methods. To assess the impact of selective serotonin reuptake inhibitors, we conducted an analysis on an observational study of a large cohort of participants with and without COPD. In order to control for the limitations of this approach, including the confounders being measured in parallel or after the exposure was implemented, we performed a rigorous statistical approach where we allowed participants to change their confounder status over time instead of assuming they stayed constant. While still potentially suffering from bias due to residual confounding, this method addresses confounding by time-variant attributes. For example, some of the exacerbations occurred during a period in which the participant had not yet been prescribed antidepressants, or had discontinued pharmacotherapy. With a time-dependent approach, events are classified according the most recent study information available [129]. Unlike logistic regression, Cox proportional hazards take into account differences across individuals in the period of risk for the outcome. For example, a person's status with regard to antidepressant use and type may change over at any time until the first exacerbation or censoring.

In conclusion, there is no evidence to support our hypothesis of participants using selective serotonin reuptake inhibitors having a lower exacerbation rate or inflammation mediating the pathway between selective serotonin reuptake inhibitors and lung function. Further research can improve upon this study by including measures of confounders prior to and after antidepressant initiation to understand the change in depression symptoms and inflammation.

## TEXT FIGURES & TABLES

Figure 4.1. Schedule of SPIROMICS study contacts

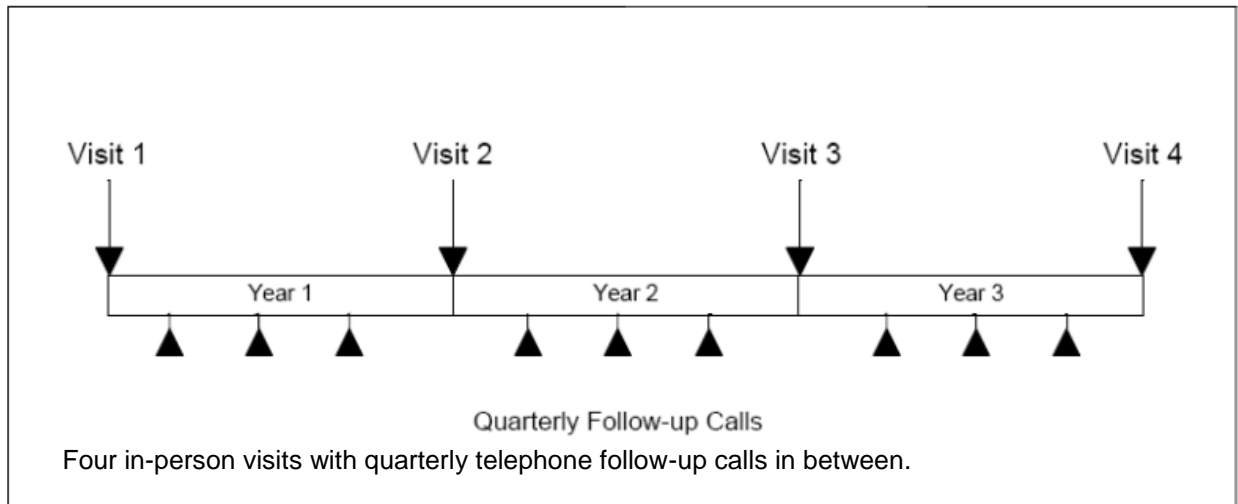


Table 4.1. SPIROMICS stratum criteria

	Non-Smokers without COPD  (stratum 1)	Smokers without COPD  (stratum 2)	Smokers with Mild/Mod COPD  (stratum 3)	Smokers with Severe COPD  (stratum 4)
Smoking status	<1 pack-year	>20 pack-years	>20 pack-years	>20 pack-years
Bronchodilator Status for Assessing Lung Function	Pre-bronchodilator	Post- bronchodilator	Post- bronchodilator	Post- bronchodilator
FEV1/FVC ratio criteria	FEV1//FVC>.7	FEV1//FVC>.7	FEV1//FVC<.7	FEV1/FVC<.7
Other Lung Function Criteria	FVC>LLN	FVC>LLN	FEV1>50% pred.	FEV1<50% pred.
Sample size	N=202	N=941	N=1207	N=624

Table 4.2. Total eligible cohort (N=2221) baseline characteristics

	<b>N or Mean±SD</b>	<b>%</b>
<b>Age, years, mean±SD</b>	64±9	
<b>Gender</b>		
<b>Male</b>	1158	52
<b>Female</b>	1063	48
<b>Race</b>		
<b>White</b>	1761	79
<b>Black</b>	361	16
<b>Asian</b>	23	1
<b>Pacific Islander</b>	51	2
<b>American Indian</b>	10	.45
<b>Mixed</b>	15	.68
<b>Height, cm, mean±SD</b>	170±10	
<b>Weight, kg, mean±SD</b>	81±18	
<b>Current or former smokers</b>		
<b>Yes</b>	760	34
<b>No</b>	1461	66
<b>Smoking history pack-years<sup>#</sup>, mean±SD</b>	48±39	
<b>FEV<sub>1</sub> % predicted, mean±SD</b>	67±27	
<b>COPD Stage</b>		
<b>None</b>	661	31
<b>Mild</b>	327	16
<b>Moderate</b>	647	31
<b>Severe</b>	331	16
<b>Very Severe</b>	138	7
<b>HADS Score, mean±SD</b>	4±3	
<b>Depressed (HADS≥8)</b>	394	18
<b>Number of exacerbations prior to enrolling</b>	0.41±0.89	

cm: centimeters, kg: kilogram; FEV<sub>1</sub>: forced expiratory volume in one second; HADS: Hospital Anxiety and Depression scale; <sup>#</sup>among ever-smokers. Shaded variables or values were not applicable for mean±SD when reporting percentage.

Table 4.3. Hazard ratios for potential confounders between selective serotonin reuptake inhibitors and exacerbations

	<b>HR for SSRIs and exacerbations</b>	<b>95% CI</b>
<b>Crude</b>	1.35	1.13 to 1.62
<b>+ Age</b>	1.36	1.13 to 1.62
<b>+ Gender</b>	1.29	1.08 to 1.55
<b>+ HADS depression score</b>	1.17	0.97 to 1.40
<b>+ Baseline FEV1</b>	1.30	1.09 to 1.56
<b>+ Prior exacerbations</b>	1.27	1.06 to 1.52
<b>+ Current smoking</b>	1.35	1.13 to 1.62
<b>+ Smoking pack-years</b>	1.37	1.14 to 1.64

Each covariate was added separately to the crude model

Table 4.4. Crude and adjusted Hazard Ratios (HRs) for time to first exacerbation using time dependent cox regression

	A. Unadjusted model		B. SSRIs and Depression		C. Adjusted model <sup>†</sup>	
	b	95% CI	b	95% CI	b	95% CI
<b>SSRI vs. No SSRIs*</b>	1.36	1.13 to 1.65	1.17	0.96 to 1.42	1.12	0.86 to 1.44
<b>Depression score</b>			1.08	1.06 to 1.10	1.04	1.01 to 1.07
<b>Age<sup>‡</sup></b>					0.97	0.85 to 1.10
<b>Gender</b>					1.42	1.16 to 1.73
<b>Baseline FEV1<sup>‡</sup></b>					0.82	0.78 to 0.85
<b>Prior Exacerbations</b>					1.42	1.32 to 1.52
<b>Current Smoker</b>					0.94	0.76 to 1.18
<b>Pack-years<sup>‡</sup></b>					1.01	0.99 to 1.03

\*indicates participants that were on other antidepressants or on no antidepressants. <sup>†</sup>Time-dependent variables included antidepressant status, current smoking status, smoking pack-years, and HADS depression score. <sup>‡</sup>Age, baseline FEV1, and pack-years are all divided by 10.

Table 4.5. Crude and adjusted Hazard Ratios (HRs) for time to first exacerbation using time dependent cox regression, excluding those without chronic obstructive pulmonary disease

	A. Unadjusted model		B. SSRIs and Depression		C. Adjusted model†	
	b	95% CI	b	95% CI	b	95% CI
<b>SSRI vs. No SSRIs*</b>	1.53	1.24 to 1.88	1.29	1.04 to 1.60	1.20	0.91 to 1.58
<b>Depression score</b>			1.08	1.06 to 1.10	1.04	1.01 to 1.07
<b>Age‡</b>					0.96	0.85 to 1.14
<b>Gender</b>					1.37	1.10 to 1.70
<b>Baseline FEV1‡</b>					0.82	0.77 to 0.86
<b>Prior Exacerbations</b>					1.39	1.29 to 1.50
<b>Current Smoker</b>					0.95	0.74 to 1.21
<b>Pack-years‡</b>					1.01	0.98 to 1.03

\*indicates participants that were on other antidepressants or on no antidepressants. †Time-dependent variables included antidepressant status, current smoking status, smoking pack-years, and HADS depression score. ‡Age, baseline FEV1, and pack-years are all divided by 10.

Table 4.6. Generalized linear regression coefficients for Baron and Kenny mediation steps for Interleukin-6 receptor as a mediator of the relationship between selective serotonin reuptake inhibitors and forced expiratory volume in one second

	A. SSRI to FEV1*		B. SSRI to IL6		C. IL6 to FEV1		D. SSRI to FEV1 controlling for IL6*	
	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Visit 1	-0.09	-4.21 to 4.04	0.01	-0.02 to 0.04	0.07	-0.10 to 0.24	-0.18	-4.31 to 3.95
Visit 2	-3.09	-11.41 to 5.22	-0.04	-0.08 to -0.01	-0.09	-0.40 to 0.21	-2.89	-11.27 to 5.49

SSRI: selective serotonin reuptake inhibitor; FEV1: forced expiratory volume in one second

\*additionally controlled for HADS depression score since this was a significant confounder between SSRI and FEV1

Table 4.7. Generalized linear regression coefficients for Baron and Kenny mediation steps for C-reactive protein as a mediator of the relationship between selective serotonin reuptake inhibitors and forced expiratory volume in one second

	A. SSRI to FEV1*		B. SSRI to CRP		C. CRP to FEV1		D. SSRI to FEV1 controlling for CRP*	
	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Visit 1	-0.09	-4.21 to 4.04	-0.05	-0.14 to 0.10	-3.60	-4.72 to -2.47	-0.28	-4.36 to 3.80
Visit 2	-3.09	-11.41 to 5.22	-0.06	-0.28 to 0.17	-4.36	-6.35 to -2.37	-3.03	-11.20 to 5.14

SSRI: selective serotonin reuptake inhibitor; FEV1: forced expiratory volume in one second

\*additionally controlled for HADS depression score since this was a significant confounder between SSRI and FEV1

## CHAPTER 5. CONCLUSIONS

The prevalence of COPD has been increasing; according to the World Health Organization, total deaths from COPD are projected to increase by more than 30% in the next 10 years [130]. While there is no cure for COPD, current treatments are focused on relieving symptoms, slowing the progression of disease and improving overall health. Bronchodilators, corticosteroids and combination bronchodilators plus inhaled glucocorticosteroids are medicines used to improve low lung function [131]. However, they can have debilitating side effects leading researchers to look for alternative treatments. Since selective serotonin reuptake inhibitors have anti-inflammatory effects and act upon serotonin, which is central in breathing control, this dissertation tested if they improve lung function and reduce the risk for pulmonary exacerbations.

Extensive literature searches across multiple electronic databases yielded 24 peer-reviewed studies that assessed antidepressants and lung function, only eight of these assessed selective serotonin reuptake inhibitors. The interpretability of these studies is hindered by methodological limitations, particularly a failure to control for important confounders or inadequate measure and testing of confounders. Results tended to vary by inclusion of participants with comorbid depression, severity of lung function impairment, and type of antidepressant. Additionally, the sample sizes were small with a large proportion (54%) having unclear or incomplete follow-up of participants or unbalanced attrition between the treatment and control groups. Furthermore, adherence rates were unrealistic since the data was not real-world but patients were being continuously followed-up and monitored. Due the potential for outcome reporting bias, small sample sizes and the plausibility of a mechanism of action, more research is needed using population-based data to provide information on the potential for certain antidepressants in improving lung function. The current study was designed to improve on prior studies, which typically reported only one measure, through its use of both objective and patient reported lung function (FEV1 and dyspnea) in two large cohorts, while controlling for important confounders. Using both objective and subjective measurements are important, as they allow us to determine not only if the lung function clinically improved, but if the participants feel better.

For the most part, this study did not support our hypothesis of an association between selective serotonin reuptake inhibitors and lung function and dyspnea; indeed, associations were in the direction of a harmful effect. In Chapter 3, we utilized the prospective information gathered in the Multi Ethnic Study of Atherosclerosis (MESA) to assess the concurrent relationship between selective serotonin reuptake inhibitors and FEV1% and dyspnea. We used two different approaches in analyzing the data, regression and difference-in-difference analyses. In both the unadjusted and adjusted linear and logistic regression analyses, selective serotonin reuptake inhibitors had an inverse association with FEV1% and increased odds of dyspnea. Adjustments included controlling for depression score, smoking status and pack-years, and other types of antidepressants. The association was moderately attenuated by the inclusion of confounders in the model, but remained negative in the fully adjusted model. The difference-in-difference results were consistent with the regression analyses in that the group who were on selective serotonin reuptake inhibitors had a significant decrease in FEV1% compared with the group who remained consistently off selective serotonin reuptake inhibitors.

It was surprising to find a relatively strong inverse association between selective serotonin reuptake inhibitors and FEV1% and dyspnea. When reviewing the literature, no studies reported an inverse association between selective serotonin reuptake inhibitors and lung function. There was one study that reported an inverse association, but the type of antidepressant was not assessed and was likely mixed, as it was a large population-based cohort [77].

One possible explanation for this inverse association was depression; although depression was controlled for through the CES-D score, we had no measure of the severity of depression prior to being on an antidepressant. Since depression is linked to increased levels of inflammation [103], it is possible that the increased inflammation seen in depression overrides the potential anti-inflammatory effects of selective serotonin reuptake inhibitors on reducing inflammation. However, in the post-hoc analysis when controlling for CES-D score alone, it had little to no effect on the crude model, which is not consistent with the argument that depression was the cause of our inverse association between selective serotonin reuptake inhibitors and lung function.

Chapter 4 built off the previous chapter and tested if selective serotonin reuptake inhibitors were associated with a lower exacerbation rate than those not on selective serotonin reuptake inhibitors. Using the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) we tested whether selective serotonin reuptake inhibitor use is associated with a reduction in pulmonary exacerbations, after adjusting for potential confounders (age, gender, smoking status and pack-years, depressive symptoms, baseline FEV1 and number of prior exacerbations), in a large cohort of both individuals with and without COPD. Similar to the results of Chapter 3, in the crude analysis, for any given visit, if a participant was using selective serotonin reuptake inhibitors they had a higher rate of first exacerbations since enrolling in the study than if they were not using selective serotonin reuptake inhibitors. When stratifying by depression score, there was still no evidence to support our hypothesis of a protective effect from selective serotonin reuptake inhibitors.

Part of the hypothesis for selective serotonin reuptake inhibitors' therapeutic effect on lung function is through a reduction in inflammation. In order to test the inflammatory hypothesis, we assessed if inflammatory markers mediate the association between selective serotonin reuptake inhibitor use and lung function. Even though selective serotonin reuptake inhibitors were not found to have a beneficial effect on FEV1, performing a mediational analysis allows us to investigate why our hypothesis did not hold: was it because selective serotonin reuptake inhibitors did not influence inflammation? Alternatively, that inflammation did not influence lung function? Investigating mediation allows us to further understand our results. The inflammatory markers were tested for their association between selective serotonin reuptake inhibitors and FEV1. Neither IL-6 nor CRP were associated with both the exposure and outcome measures. IL-6 was associated with selective serotonin reuptake inhibitors only at visit 2, but was not associated with FEV1 during either time period. CRP was consistently associated with FEV1 at visit 1 and visit 2, but not with selective serotonin reuptake inhibitors at any point. This leads us to believe that selective serotonin reuptake inhibitors do not influence these anti-inflammatory markers enough to cause an increase in lung function. Additionally, since selective serotonin reuptake inhibitors were not associated with inflammatory markers, they are not causing an *increase* in the inflammatory response, leading to the inverse association with lung function (lower lung function). Further studies are needed to elucidate this inverse association between selective serotonin reuptake inhibitors and lung function. If selective serotonin reuptake inhibitors

truly do lower lung function, this should be noted and the risks and benefits weighted for individual patients and their needs with their practitioners.

There were no interventional studies found in the literature that supported the hypothesis of selective serotonin reuptake inhibitors improving lung function. However, tianeptine was found to reduce symptoms and increase pulmonary function in children with asthma [74]. Tianeptine is a selective serotonin reuptake enhancer; instead of inhibiting the uptake of serotonin, like a selective serotonin reuptake inhibitor, it increases the uptake of serotonin, lowering serotonin's activity. Since tianeptine has the opposite effect on serotonin, this suggests that the effects of serotonin on lung function may not be as clear as we hoped and that further study is warranted. It is possible that an increase in serotonin is harmful to lung function, instead of being beneficial. It is also possible that we are seeing reverse causation. Although we controlled for prior exacerbations, indicating severity of disease, control may be insufficient. Participants with worse disease may be more likely to be depressed, leading to use of a selective serotonin reuptake inhibitor, which is why we are seeing selective serotonin reuptake inhibitors having an inverse association with lung function.

Although this study addresses weaknesses evident in the existing literature, this project had its own limitations. In both MESA and SPIROMICS, the specific brand of antidepressant was not assessed (other than antidepressant class) nor the dose. While drugs in an antidepressant class have a similar chemical make-up, other fillers and additives may change their effects on lung function. For example, in Chapter 2, open-label studies investigating citalopram and fluoxetine consistently had positive associations. The dose of the medication would allow us to assess if a certain dosing level is needed for the anti-inflammatory effects of antidepressants to affect lung function. Additionally, we would ideally like our mediational analysis to have longitudinal data (where the visits are separated by a maximum of a few months) where our independent variable preceded the mediational variable and the mediational variable precedes the dependent variable in order to establish temporality. However, in these data the independent variable (selective serotonin reuptake inhibitors) and the mediational variable (inflammatory markers) were taken at the same exam. If we were to use the longitudinal data, our sample sizes would be severely diminished, since there was a large drop in the number of participants who had blood draws at visit 2. Additionally, the

timing of the measurement is spaced out by a year or more, which is unlikely to be relevant as we hypothesize a concurrent effect. Lastly, controlled for depression under the theory that is a confounding variable in the relationship between selective serotonin reuptake inhibitors and lung function. If SSRIs work through directly on inflammation (depression causes SSRI use -> SSRIs directly improve inflammation and lung function), then depression would be seen as a confounder. However, it is also possible that depression is a mediator in the relationship between selective serotonin reuptake inhibitors and lung function.

Despite these limitations, the current project has several notable strengths. It provides novel information on the effects of selective serotonin reuptake inhibitors on spirometry, dyspnea, and pulmonary exacerbations. It highlights that antidepressants may not be as safe as previously thought in patients with low lung function, and encourages further investigation into this relationship. Depression is a common comorbidity among individuals with low lung function, signifying that antidepressant use may be significant in this population. If these antidepressants are worsening lung function, it is pertinent for caregivers to be aware of the potential side effects to carefully weigh the risks and benefits of antidepressant treatment.

In addition to the potential clinical application of the information generated from our analyses, this dissertation adds to the literature on selective serotonin reuptake inhibitors and their effects on lung function in general. We were able to investigate the association of selective serotonin reuptake inhibitors on spirometry, dyspnea and pulmonary exacerbations in two large cohorts that included individuals with diagnosed COPD. Our inclusion of multiple confounders represents an improvement over prior work, which were limited in their adjustment and follow-up of participants.

Future studies should explore differences in reduced low lung function due to genetic susceptibility or smoking-induced disease since the inflammatory markers may vary as the cause of the disease is different. If future studies replicate these results and selective serotonin reuptake inhibitors are found to have an inverse association with lung function, then we recommend a larger meta-analysis and an oversight committee in order to formulate guidelines. It is likely that the benefits and side effects will need to be weighted between patients and their healthcare providers.

In conclusion, although small, poorly controlled studies have shown a beneficial association between selective serotonin reuptake inhibitors and lung function, we found an inverse association between selective serotonin reuptake inhibitors and spirometry, dyspnea and pulmonary exacerbations. Overall, the results suggest that selective serotonin reuptake inhibitors may not be beneficial for individuals with low lung function, and may even be harmful. Further research in the form of prospective, interventional trials is ideal to further elucidate this in order to make recommendations for the treatment of patients with low lung function, but questionable given the results that selective serotonin reuptake inhibitors may harm lung function. We suggest analyses in the form of observational studies to first determine if the results of these studies can be replicated.

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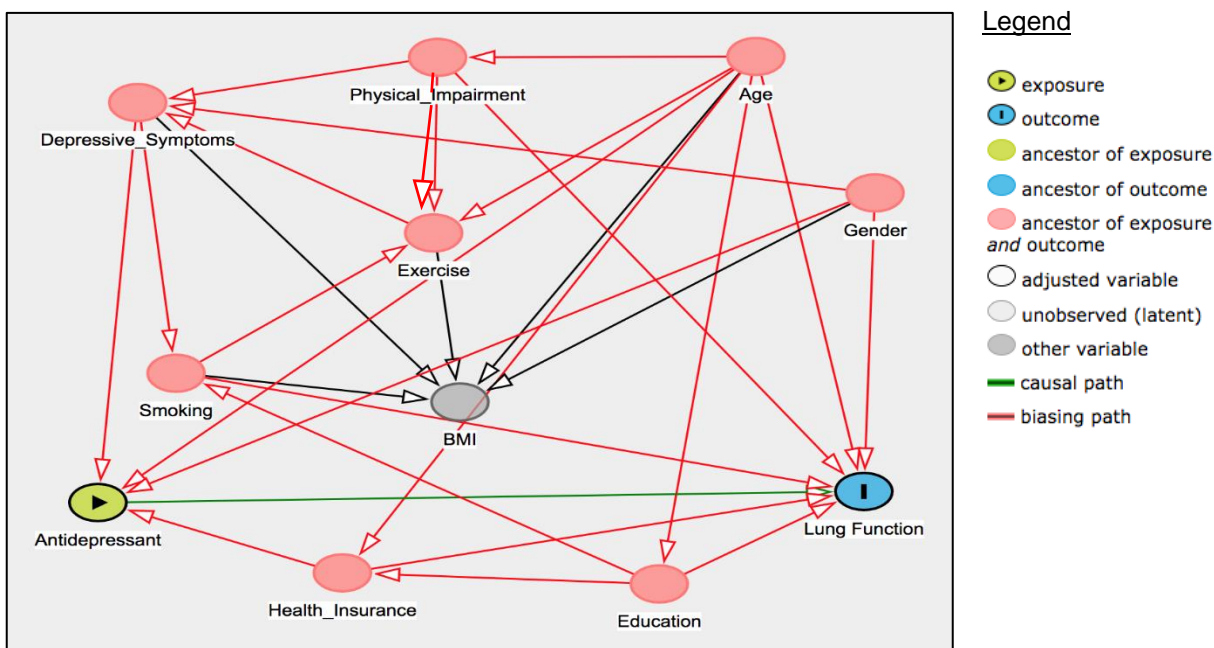
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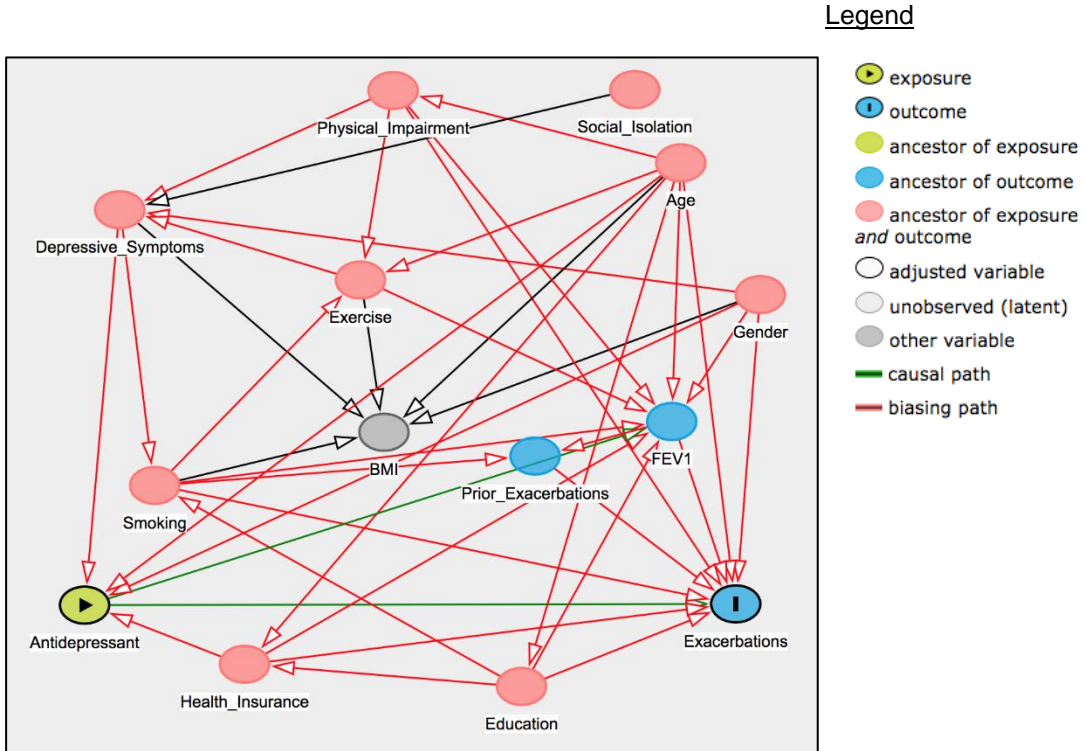
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## APPENDICES

Appendix Figure 1. Directed Acyclic Graph for hypothesized confounders with lung function in the MESA study



Appendix Figure 2. Directed Acyclic Graph for hypothesized confounders with exacerbations in the SPIROMICS study



Appendix Table 1. Criteria for risk of bias assessment

<b>Domains</b>	<b>Prompting items for consideration</b>
<b>Study participation</b>	<ul style="list-style-type: none"> <li>a. Adequate participation in the study by eligible persons</li> <li>b. Description of the source population or population of interest</li> <li>c. Description of the baseline study sample</li> <li>d. Adequate description of the sampling frame and recruitment</li> <li>e. Adequate description of the period and place of recruitment</li> <li>f. Adequate description of inclusion and exclusion criteria</li> </ul>
<b>Study Attrition</b>	<ul style="list-style-type: none"> <li>a. Adequate response rate for study participants</li> <li>b. Description of attempts to collect information on participants who dropped out</li> <li>c. Reasons for loss to follow-up are provided</li> <li>d. Adequate description of participants lost to follow-up</li> <li>e. There are no important differences between participants who completed the study and those who did not</li> </ul>
<b>Outcome Measurement and Reporting</b>	<ul style="list-style-type: none"> <li>a. A clear definition of the outcome is provided</li> <li>b. Method of outcome measurement used is adequately valid and reliable</li> <li>c. The method and setting of outcome measurement is the same for all study participants</li> <li>d. There is no selective reporting of results</li> </ul>
<b>Study Confounding</b>	<ul style="list-style-type: none"> <li>a. All important confounders are measured</li> <li>b. Clear definitions of the important confounders measured are provided</li> <li>c. Measurement of all important confounders is adequately valid and reliable</li> <li>d. The method and setting of confounding measurement are the same for all study participants</li> <li>e. Appropriate methods are used if imputation is used for missing confounder data</li> <li>f. Important potential confounders are accounted for in the study design</li> <li>g. Important potential confounders are accounted for in the analysis</li> </ul>

Appendix Table 2. Methods of dyspnea assessment

<b>Study</b>	<b>Method</b>
Brown 2005	Asthma control questionnaire
Brown 2012	Asthma control questionnaire
Borson 1992	100-mm horizontal visual analog scale before and after 12-minute walk test; Pulmonary Function Status Instrument
Carroll 1990	Visual Analog Scale (VAS)
Eiser 2005	Diary card data recording nocturnal waking's due to dyspnea, and breathlessness and effect of breathlessness on quality of life
Grove 1995	Borg during 6-minute walk test; activity questionnaire in which for fifty common activities they were asked to specify if a daily activity was avoided or interrupted because of breathlessness.
Lacasse 2004	Chronic Respiratory Questionnaire
Momtaz 2015	Modified Borg Scale
Perna 2004	Modified Borg Scale
Strom 1995	Graded on a six step scale, ranging from 0=no dyspnea to 6=dyspnea
Sugihara 1965	Specific scale not reported

Appendix Table 3. Detailed results of each study

Adams, C., et al.

After one, two and three years of amitriptyline treatment lung functions of cystic fibrosis participants, measured as FEV1 % predicted, improved significantly in the treatment group (Table and Figure below)

Treatment	Number of participants	Year before	Baseline before amitriptyline studies	Year after 1	Year after 2	Year after 3	p-value
Amitriptyline	20	61.5±18.5	61.5±16.9	68.7±20.3	-	-	0.001
		Differences	-0.5±4.4	7.6±7.0	-	-	0.0008
	12	57.3±18.6	59.8±18.5	65.9±21.7	64.9±22.2	-	0.009
		Differences	2.2±2.4	6.5±7.9	5.6±10.3	-	0.075
	5	55.3±23.8	56.8±23.5	64.3±26.1	64.4±25.0	64.5±25.7	0.050
		Differences	1.5±2.3	7.6±7.4	7.6±7.4	7.7±8.0	0.07
Controls	14	70.0±17.4	65.8±24.0	65.6±17.8	-	-	0.010
		Differences	-2.6±5.1	-1.8±3.3	-	-	0.32
	10	65.5±16.0	63.7±17.0	61.8±16.5	61.6±16.9	-	0.051
		Differences	-1.8±5.9	-1.9±3.0	-2.1±3.7	-	0.45
	5	64.3±20.0	63.1±20.4	62.1±19.1	61.7±22.5	62.1±21.1	0.075
		Differences	-1.2±7.0	-1.0±3.9	-1.4±3.0	-1.0±1.3	0.48
FEV1 % predicted efficacy of amitriptyline in participants with cystic fibrosis at baseline, the year before, one year after, after two and three years of amitriptyline treatment compared to controls.							

Borson, S., et al.

No difference between groups. Pulmonary function numbers not reported. Antidepressant treatment did not substantially affect dyspnea during day-to-day activities; there was however associated with small improvement of dyspnea during activities requiring little energy; did not improve during 12 minute walk.

Assessment Point	Placebo (n=11)	Nortriptyline (n=13)	Differential Treatment Effect
During 81 activities of daily living			
Low demand			
Entry	2.1±1.8	2.7±1.8	0.37±0.28
Exit	1.9±1.6	2.1±1.5*	
Moderate demand			
Entry	4.3±2.5	5.2±2.5	0.22±0.58
Exit	4.2±2.6	5.0±2.5	
High demand			
Entry	5.2±2.8	6.8±2.7	0.70±0.69
Exit	5.3±2.9	6.2±3.0	
*p=0.04			

*Brown, E.S., et al. (2005)*

There were no significant differences between the citalopram and placebo group in change in ACQ ( $-7.1 \pm 7.6$  vs  $-8.5 \pm 10.1$ ,  $p=0.47$ ).

Changes in asthma outcomes were similar between the groups. However, the citalopram group required less systemic corticosteroids during the trial. This finding is of clinical importance as systemic corticosteroid therapy is associated with numerous side effects and is a marker for severe asthma exacerbations.

*Brown, E.S., et al. (2012)*

The combined asthma control questionnaire (ACQ) scores did not improve significantly in the initial effect ( $t_{20}=0.2$ ,  $p=0.86$ ) or in the slope ( $F_{1,18}=0.6$ ,  $p=0.4548$ ). Similarly, no significant between-group differences were found in the initial effect or the slope (table below). The effect size at week 12 was small (0.24).

Outcome Measure	F Value	p-value	Effect size
ACQ total score			
Initial effect: week 0-1	F (1,21)=0.3	0.6052	
Slope: week 1-12	F(1,17)=<0.01	0.9852	0.24

*Carroll, N., et al.*

No statistical difference in visual analog scale (VAS) (dyspnea questionnaire) completed by participants. A small increase was noted during the placebo limb when the same scale was completed independently by the spouse. The median VAS registered by the spouse was 47 (range 34-82) at entry, 54 (range 35-77) on placebo and 46 (range 12-68) on protriptyline ( $p<0.01$ ).

No difference between groups for spirometry. No numbers reported for FEV1, although authors state that full pulmonary function tests were performed.

Eiser, N., et al. (2005) (crossover)

Dyspnea numbers not reported for the double-blinded study.

No difference between groups for spirometry outcome.

	Active Paroxetine			Placebo			p <sup>2y</sup>
	Baseline	Post Rx	p	Baseline	Post Rx	p	
FEV1	1.13±0.64	1.12±0.69	0.430	1.15±0.68	1.13±0.62	0.298	0.417
FVC	2.54±0.82	2.57±0.86	0.407	2.74±1.12	2.72±1.01	0.360	0.345
RV	4.06±1.21	3.71±1.21	0.082	3.92±1.18	3.52±1.64	0.211	0.295

*p taken from paired t-tests comparing within-subject effect of treatment; p<sup>2y</sup> taken from unpaired t-tests compares differences produced by active treatment and placebo between groups*

Eiser, N., et al. (2005) (cohort)

No difference between groups for spirometry or dyspnea.

	Baseline	Post Rx	p-value
FEV1	1.14±0.65	1.18±0.70	0.219
FVC	2.64±0.97	2.71±0.90	0.367
RV	4.06±1.21	3.52±1.64	0.480
Dyspnea	3.19±0.50	3.10±0.71	0.300

Gordon, G.H., et al.

FEV1 and FVC tended to be higher after treatment compared with placebo, but no statistical significance was seen.

	Baseline	Desipramine	Placebo
FEV1 (ml)	775±262	770±277	657±255
FVC	1820±470	2066±655	1753±491

Grove, A., et al.

No effect of mianserin, prednisolone (corticosteroid) did increase FVC however.

	FEV <sub>1</sub> (l)	FVC (l)	Borg Scale
Baseline	0.92	2.53	12 (11-13)
Placebo	0.90 (0.83-0.97)	2.17 (2.03-2.30)	12.5 (11-13)
Prednisolone	0.91 (0.85-0.98)	2.42 (2.28-2.56)*	11.5 (11-13)
Mianserin	0.82 (0.75-0.88)	2.19 (2.06-2.32)	12.5 (11-13)
*Significantly different from both placebo and mianserin			

Lacasse, Y., et al.

The unadjusted changes in the Chronic Respiratory Questionnaire at follow-up showed improvements favoring treatment for dyspnea. However, this did not reach statistical significance. No numbers are reported, just figures.

Lechin, F., et al.

Tianeptine but not placebo provoked a dramatic and sudden decrease of clinical severity ratings (breathlessness) and an increase of FEV<sub>1</sub> ( $p < 0.0001$ ). No numbers given, only figures.

Light, R.W., et al.

No difference between groups.

	Baseline	Placebo	Doxepin Hydrochloride
FEV <sub>1</sub> (L)	0.87±0.30	0.82±0.25	0.80±0.21
FVC (L)	2.45±0.55	2.22±0.45	2.16±0.52

Meares, R.A., et al.

Eleven of the 12 participants showed a significant improvement in FEV<sub>1</sub> after the intramuscular administration of amitriptyline ( $p < 0.002$ ). Mean improvement of whole group was 17% (from 2.02 to 2.37L) (Improvement ranged from 11-47%). In the remaining patient that did not have an increase in FEV<sub>1</sub>, her initial FEV<sub>1</sub> was above the expected value of one of her height and sex.

Momtaz, O.M., et al.

Dyspnea and spirometric parameters were significantly improved in group I participants who had received antidepressant/anti-anxiolytic therapy but not in the non-treated group II participants. Dyspnea actually increased in the group II participants.

Group I-treated group			
	At the start	3 months later	p-value
FVC (L/s)	2.08±0.54	2.18±0.55	0.01
FEV <sub>1</sub> (L/s)	1.10±0.49	1.20±0.44	0.01
Dyspnea	4.36±0.99	3.68±1.09	0.001

Group II-non-treated group			
	At the start	3 months later	p-value
FVC (L/s)	1.86±0.44	1.83±0.41	0.50
FEV <sub>1</sub> (L/s)	1.06±0.38	1.04±0.29	0.80
Dyspnea	4.50±1.01	5.17±0.99	0.001

Nahrlich, L., et al.

Fev1 improved (both absolute and relative to baseline) in both the ITT and PP population. In contrast, placebo treatment resulted in a decrease in FEV.

Population	Treatment group	Number of participants	FEV1 % absolute to baseline	p-value	FEV1 % relative to baseline	p-value
Intent to treat	Amitriptyline	19	+0.6±5.7	0.034	+0.2±11.4	0.08
	Placebo	17	-3.8±6.9		-6.1±11.5	
Per protocol	Amitriptyline	16	+2.2±5.2	0.013	+3.6±7.9	0.013
	Placebo	13	-2.7±5.0		-4.9±10.1	

*Nascimento, I., et al.*

Higher values of FEV1 in participants on antipanic drugs than when they were in the washout period; this persisted even after inhalation of bronchodilator.

Panic disorder participants on antipanic drugs				
	Before salbutamol		After salbutamol	
	Observed	% predicted	Observed	% predicted
FVC (L)	4.31±0.95	104.63±12.66	4.31±0.94	104.72±12.24
FEV1 (L)	3.58±0.71	107.09±13.74	3.66±0.75	109.27±13.54
Panic disorder participants without antipanic drugs				
	Before salbutamol		After salbutamol	
	Observed	% predicted	Observed	% predicted
FVC (L)	4.15±0.85	102.90±11.64	4.16±0.92	102.90±12.42
FEV1 (L)	3.42±0.67*	101.81±14.40*	3.54±0.70	105.18±13.25*
*significantly different from value with antipanic drug (p<0.05)				

*Papp, L.A., et al.*

No significant change in spirometric indices. Pulmonary function numbers not reported.

*Perna, G., et al.*

All participants showed improved respiratory function measures and a strong decrease in breathing discomfort (percentage of decrease in score on the BORG scale=54±16%).

	One month before	Immediately before	After one month of citalopram	p-value
FEV1	0.93±0.13	0.91±0.17	1.12±0.15	p<0.05
Borg scale score	7.5±1.0	7.7±1.4	3.5±1.4	p<0.05

Riethmuller, J., et al.

After 14 days of treatment, FEV1 had improved significantly in the 25 mg/d amitriptyline group relative to placebo (p=0.048. No significant change in lung function was observed when participants took 50 and 75mg of amitriptyline.

Treatment group	Number of participants	Dose of amitriptyline (mg)	Absolute	Relative	Slopes	p-value
Placebo	13	0				
Amitriptyline	7	25	+3.0±4	+4.0±7	+1.5±2	0.048
Amitriptyline	8	50	+0.7±3	+0.6±9	+0.4±2	0.28
Amitriptyline	8	75	-0.7±4	-0.06±9	+0.3±2	0.79
Amitriptyline	23	25-75	+1.0±4	+1.5±8	+0.7±2	0.07

Series, F., et al. (1989)

No change.

	Baseline	2 weeks	10 weeks
FEV1%	40.8±3.9	42.4±4.6	46.0±3.9
FVC%	56.0±2.9	59.2±2.5	59.2±2.7

Series, F., et al. (1993)

There were no significant changes in expiratory flow.

	Control			Treated		
	Baseline	10 weeks	Follow-up	Baseline	10 weeks	Follow-up
FEV1 (L)	0.90±0.14	0.98±0.16	0.99±0.16	1.04±0.12	1.21±0.10	1.11±0.14

*Strom, K., et al.*

Neither protriptyline nor placebo had any impact on the dyspnea score.

No difference between groups.

	Baseline Protriptyline	Baseline Placebo	p-value	Protriptyline	Placebo	p-value
FEV1 (L)	0.6±0.2	0.7±0.2	NS	0.7±0.3	0.7±0.3	NS

*Sugihara, H., et al.*

In total, 62% observed an excellent or good therapeutic effect, 38% experienced a poor effect.

						Summary	
	Excellent (+++)	Good (++)	+	Poor (±)	-	Good to Excellent	Poor
In adults							
Males (41)	7	6	11	6	11	24 (59%)	17 (41%)
Females (19)	1	8	4	1	5	13 (68%)	6 (32%)
All (60)	8 (13%)	14	15	7	16	37 (62%)	23 (38%)
In children under 15 (14 participants, 11 males and 3 females)	2 (14%)	4 (29%)	5 (36%)	2 (14%)	1 (7%)	11 (79%)	3 (21%)

Excellent (+++)-Subjective and objective symptoms disappeared completely

Good (++) : Steroid therapy was withdrawn successfully and dyspnea disappeared but wheezing remained;  
or (+) Dosage of steroid hormone was reduced to one-third and the number of attacks decreased or  
dyspnea improved.

Poor (±): No response was observed or is some improvement was observed, it could not be considered to  
be the effect of the drug, (-)-Symptoms were aggravated because of the side effects.

Van Milligen, B.A., et al.

Women with higher depressive symptom severity and women using antidepressants had significantly poorer lung function. This was not true for men. Actual number of FEV1 not given, only beta associations.

	Men (n=543)		Women (n=1086)	
	B ( $\pm$ S.E.)	p	B ( $\pm$ S.E.)	p
Depression	Reference		Reference	
Use of antidepressants	7.08 ( $\pm$ 8.9)	0.43	-10.94 ( $\pm$ 4.9)	0.03

Appendix Table 4. Detailed attrition results

Study	Treatment group	Control group
Adams 2016	<b># who left:</b> 8 participants (40%) left in the second year and an additional 7 (75%) in the third <b>reason:</b> not reported	<b># who left:</b> 4 (28.6%) participants left in the second year and an additional 5 (64% total) in the third <b>reason:</b> not reported
Borson 1992	<b># who left:</b> 5 (27.8%) <b>reason:</b> 3 for side effects of drug (dry mouth, sedation, and/or orthostatic hypotension); 2 for non-drug related reasons	<b># who left:</b> 1 (5.6%) <b>reason:</b> died of cardiopulmonary arrest
Brown 2005	<b># who left:</b> 8 <b>Reason:</b> it is unclear if these 8 were part of the placebo or control group.	<b># who left:</b> 8 <b>Reason:</b> it is unclear if these 8 were part of the placebo or control group.
Brown 2012	<b># who left:</b> 1 <b>reason:</b> 1 participant had no post-baseline data, but it is not clear if they were in the treatment or placebo group	<b># who left:</b> 1 <b>reason:</b> 1 participant had no post-baseline data, but it is not clear if they were in the treatment or placebo group
Carroll 1990	<b># who left:</b> 0 <b>reason:</b> not applicable	<b># who left:</b> 1 (5.6%) <b>reason:</b> died
Eiser 2005	<b># who left:</b> none <b>reason:</b> 4 participants who had drawn active antidepressant treatment developed side effects on paroxetine- nausea and vomiting- and finished study in single-blind fashion taking Lofepamine 140 mg.	<b># who left:</b> 0 <b>reason:</b> not applicable
Eiser 2005 (open-label)	<b># who left:</b> 0 <b>Reason:</b> 1 patient who had drawn placebo initially developed nausea on the open Paroxetine and continued in the open-label portion on Dothiepin 150 mg daily. 2 participants, 1 initially on active and 1 on placebo, did not improve when on active paroxetine, despite increase to 40mg. Therefore, their treatment was changed to Dothiepin 150mg daily for open label.	not applicable-no control group
Gordon 1985	<b># who left:</b> 2 (15.4%) <b>reason:</b> 1 had intolerable side effects (not explicitly stated) and 1 had new onset of multifocal atrial tachycardia	<b># who left:</b> 5 (38.5%) <b>reason:</b> 4 of these were hospitalized (2 with severe exacerbations of COPD, 1 with myocardial infarction, and 1 with ventricular arrhythmias) and 1 moved
Grove 1990	<b># who left:</b> 0 <b>reason:</b> not applicable	<b># who left:</b> 0 <b>reason:</b> not applicable
Lacasse 2004	<b># who left:</b> 7 (58.3%) <b>reason:</b> 1 died before starting, 3 discontinued intervention, 2 refused to continue, 1 had side effects (tremor)	<b># who left:</b> 7 (63.6%) <b>reason:</b> 1 died before starting, 3 discontinued intervention, 2 refused to continue, 1 had severe exacerbation
Lechin 1998	<b># who left:</b> 13 (15.9%)	<b># who left:</b> unknown

	<b>Reason:</b> 5 left due to failure to follow protocol; 5 dropped out due to lack of motivation (3 <sup>rd</sup> and 4 <sup>th</sup> weeks); 3 ruled out before first week because of epileptiform abnormalities. Authors did not indicate whether participants dropped in the treatment or placebo phase.	<b>Reason:</b> Authors did not indicate whether participants dropped in the treatment or placebo phase.
Light 1986	<b># who left:</b> 3 (25%) <b>reason:</b> intolerable drowsiness, blurry vision and nausea and vomiting	<b># who left:</b> 0 <b>reason:</b> not applicable
Meares 1971	<b># who left:</b> 0 <b>reason:</b> not applicable	not applicable-no control group
Nahrlich 2013	<b># who left:</b> 2 (9.5%) from ITT, additional 3 (23.8%) from PP <b>reason:</b> 2 excluded from ITT analysis (1 refused medication, 1 had high C-reactive protein); an additional 3 were excluded from the PP analysis (2 had high C-reactive protein, 1 was not correctly medicated)	<b># who left:</b> 2 (10.5%) from ITT, an additional 4 (31.6%) from PP <b>reason:</b> 2 excluded from ITT analysis (one due to missing lung function follow-up value, one due to high CRP); an additional 4 were excluded from the PP analysis due to high CRP
Nascimento 2009	<b># Who left:</b> 1 (8%) <b>reason:</b> did not participate	not applicable- no control group
Momtaz 2015	<b># who left:</b> 0 <b>reason:</b> not applicable	<b># who left:</b> 0 <b>reason:</b> not applicable
Papp 1995	<b># who left:</b> 0 <b>reason:</b> not applicable	not applicable- no control group
Perna 2004	<b># who left:</b> 0 <b>reason:</b> not applicable	not applicable- no control group
Riethmuller 2009	<b># who left:</b> 7 (37%) <b>reason:</b> 1 patient discontinued treatment after 10 days due to an adverse event (authors do not report what treatment they were on); 6 participants were excluded from the analysis according to criteria of study plan (dose reduction or exacerbation)	<b># who left:</b> 7 (37%) <b>reason:</b> 1 patient discontinued treatment after 10 days due to an adverse event (authors do not report what treatment they were on); 6 participants were excluded from the analysis according to criteria of study plan (dose reduction or exacerbation)
Series 1989	<b># who left:</b> 2 (14.3%) <b>Reason:</b> 2 participants were excluded before the second visit because the treatment for the COPD had changed; the week 2 study was not carried out in two participants because of technical problems, and 1 participants who developed bronchopneumonia. Therefore, data is presented on 12 participants, 10 at 2 weeks and 11 at 10 weeks.	not applicable- no control group
Series 1993	<b># who left:</b> 0 <b>Reason:</b> The authors note a range of follow-up times, but say that they were the same on average between the treated and control groups.	<b># who left:</b> 0 <b>reason:</b> not applicable

Strom 1995	<p><b># who left:</b> 3 (21.4%)</p> <p><b>reason:</b> 2 for medication side effects (dry mouth, visual disturbance, dizziness and fatigue) and 1 for exacerbation of COPD</p>	<p><b># who left:</b> 0</p> <p><b>reason:</b> not applicable</p>
Sugihara 1965	<p><b># who left:</b> unknown</p> <p><b>reason:</b> Reports that drug had to be withdrawn in some participants but does not give specific number</p>	not applicable-no control group
Van Milligen 2011	<p><b># who left:</b> 0</p> <p><b>reason:</b> not applicable</p>	<p><b># who left:</b> 0</p> <p><b>reason:</b> not applicable</p>

Appendix Table 5. Risk of bias assessment for each study

*Adams., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	Follow-up based off previously randomized study. 20 out of the 59 participants from the original study asked for continuing amitriptyline treatment, since they volunteered it is likely that they had a favorable effect during the first trial, which is why they wanted to continue therapy.	High risk
Study Attrition	Over three years 75% left treatment group and 64% left control group	High risk
Outcome Measurement and Reporting	All pre-defined outcomes are reported	Low risk
Study Confounding	Both groups were similar with regard to gender, age, weight, lung function parameters, pancreatic sufficiency, and chronic bacterial infections.	Low risk

*Borson, S., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	moderate to severe COPD and coexisting depression	Low risk
Study Attrition	3 participants left the trial because of side-effects and 2 discontinued for non-drug related reasons (27.8% of treatment group); 1 died of cardiopulmonary arrest while receiving placebo (5.6% of placebo group)	High risk
Outcome Measurement and Reporting	No reporting of exact spirometry measures, even though they were an outcome of the study. However, many measures were collected and the authors likely did not have room to show non-significant improvements.	High risk
Study Confounding	Randomized; Assignment to treatment condition was performed by pharmacist blind to study questions using a table of random numbers; Pharmacy-controlled. All personnel blind to medication assignment	Low risk
Other	Although not significant, baseline FEV <sub>1</sub> was different between treatment and control groups; Pill counts, weekly patient reports and serum drug levels	Low risk

Brown, E.S., et al (2005)

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	out patients with asthma and current major depressive disorder	Low risk
Study Attrition	Unclear	Unclear
Outcome Measurement and Reporting	All pre-defined outcomes are reported	Low risk
Study Confounding	Randomized; Double blind -Medication or placebo in identical appearance	Low risk
Other	Increased dosage for those who showed no response	High risk

Brown, E.S., et al (2012)

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	out patients with asthma, major depressive disorder and at least 1 course of oral corticosteroids in the prior 12 months	Low risk
Study Attrition	Unclear	Unclear
Outcome Measurement and Reporting	All pre-defined outcomes are reported	Low risk
Study Confounding	Randomized using a randomization program (random number sequence); Double blind-Medication or placebo in identical appearance	Low risk
Other	Increased dosage for those who showed no response	High risk

Carroll, N., et al.

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	severe disease (FEV <sub>1</sub> <40%) and previously documented hypercapnia while stable	Low risk
Study Attrition	One male patient died during second phase (placebo) and was excluded from analysis. No discontinuations from side-effects	Low risk
Outcome Measurement and Reporting	No numbers reported for spirometry measures, even though they are an outcome of the study.	High risk
Study Confounding	Randomized study, randomization method not described; Double-blinded trial. The exact method is not described.	Low risk
Other	No-washout period, no mention of patient compliance	High risk

Eiser, N., et al.

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	clinical depression; well-documented, stable COPD; no psychotropic drugs within 3 months	Low risk
Study Attrition	Four participants who had initially drawn active anti-depressant treatment developed significant side effects on Paroxetine and finished study taking Lofepamine 140 mg in a single-blind fashion.	High risk
Outcome Measurement and Reporting	Dyspnea measure not reported	High risk
Study Confounding	Randomized study, randomization method not described; double-blinded; researchers did not have access to the previous measurements of lung function	Low risk

Eiser, N., et al. (open-label)

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	All participants from randomized crossover study	Low risk
Study Attrition	1 patient who had drawn placebo initially developed nausea on the open Paroxetine and continued in the open-label portion on Dothiepin 150 mg daily. 2 participants, 1 initially on active and 1 on placebo, did not improve when on active paroxetine, despite increase to 40mg. Therefore, their treatment was changed to Dothiepin 150mg daily for open label.	High risk
Outcome Measurement and Reporting	All outcomes reported	Low risk
Study Confounding	It was decided it was unethical to withhold treatment for depression longer than 6 weeks, after the RCT portion (above), all participants continued taking paroxetine 20mg daily in an open fashion until all participants had received 3 months of treatment	Low risk
Other	No mention of patient compliance	Low risk

Gordon, G.H., et al.

Domain	Description	Review author's judgment
Study Participation	stable state and FEV <sub>1</sub> < 1 liter	Low risk
Study Attrition	Of the original 13 participants, 7 left the study before its completion; 5 of them were in placebo group; only report on 6 that completed	High risk
Outcome Measurement and Reporting	All pre-specified outcomes are reported.	Low risk
Study Confounding	Order of drugs assigned randomly by hospital pharmacy; Double-blinded. Pharmacy controlled blinding.	Low risk
Other	Maximum tolerated dose given or 100 mg, not standardized; Pill counts and medication diaries	High risk

Grove, A., et al.

Domain	Description	Review author's judgment
Study Participation	out patients with stable COPD (FEV <sub>1</sub> <60% with less than 15% reversibility after salbutamol)	Low risk
Study Attrition	No dropouts	Low risk
Outcome Measurement and Reporting	Results not reported on functional assessment questionnaire	High risk
Study Confounding	Randomized trial; double blind	Low risk

Lacasse, Y. et al.

Domain	Description	Review author's judgment
Study Participation	home care COPD participants (FEV <sub>1</sub> ≤50%) who are depressed	Low risk
Study Attrition	14 participants left trial, 7 in treatment group and 7 in placebo group	High risk
Outcome Measurement and Reporting	All outcomes reported	Low risk
Study Confounding	Randomized trial; double blind	Low risk
Other	Maximum of 20mg or highest dose not associated with any side effect; only figures given, no numbers reported; pill counts	High risk

*Lechin, F., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	children with asthma, FEV <sub>1</sub> <70%	Low risk
Study Attrition	Unclear at which stage (treatment or placebo) the participants dropped out	Unclear
Outcome Measurement and Reporting	All pre-defined outcomes are reported, but no numbers are presented, only figures	High risk
Study Confounding	Randomized, method not given; Double-blinded. Interviewers were unaware of the participants treatment group; identical dark capsules; crossover design	Low risk

*Light, R.W., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	FEV <sub>1</sub> <1.25 L and FEV <sub>1</sub> /FVC <50%; no major antipsychotic drugs and tricyclic antidepressant within 2 months; had depression and anxiety	Low risk
Study Attrition	3 participants left study due to side-effects of drug	High risk
Outcome Measurement and Reporting	All outcomes reported	Low risk
Study Confounding	Double-blind; crossover design	Low risk
Other	Various dosing of doxepin given (150mg max, if side effects occurred- dose was decreased)	High risk

*Meares, R.A., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	12 asthmatics from medical outpatient clinic, not selected in any way	Low risk
Study Attrition	None	Low risk
Outcome Measurement and Reporting	All-pre-defined outcomes are reported	Low risk
Study Confounding	No control	High risk
Other	It is unclear if the participants knew when they were getting the saline injection versus the drug	High risk

Momtaz, O.M., et al.

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	No mention of how participants were chosen for which group; severe COPD with depression and/or anxiety	High risk
Study Attrition	no dropouts	Low risk
Outcome Measurement and Reporting	All pre-specified outcomes are reported.	Low risk
Study Confounding	Matched study, no randomization mentioned by authors	High risk
Other	Matched on sex, all were stage II or IV COPD	Low risk

Nahrlich, L., et al.

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	cystic fibrosis participants >14 years of age, FEV1 >30% and <90%	Low risk
Study Attrition	There was an error in the randomization so one patient in treated group received placebo and one patient in placebo group received treatment.	High risk
Outcome Measurement and Reporting	All pre-defined outcomes are reported, both ITT and PP analyses are reported	Low risk
Study Confounding	Randomized using statistical software; Double-blinded; placebo was corn-starch capsules	Low risk
Other	Authors report 21 assigned to treated, 19 assigned to control, 19 treated and 17 controls for ITT, and 16 treated and 13 controls for PP, however the baseline characteristics table reports 19 treated and 18 control (it is unclear if this is a typo)	High risk

*Nascimento, I., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	panic disorder participants with or without agoraphobia; in good physical condition, no past or current diagnosis of respiratory disorders, no history of smoking	Low risk
Study Attrition	1 participant refused to participate in follow-up	Low risk
Outcome Measurement and Reporting	All pre-defined outcomes were reported	Low risk
Study Confounding	No control; single-blind	High risk
Other	Participants were on multiple medications, making it hard to determine which drug had the effect	High risk

*Papp, L.A., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	COPD participants with and without comorbid anxiety recruited from an outpatient pulmonary clinic	Low risk
Study Attrition	No dropouts	Low risk
Outcome Measurement and Reporting	No specific numbers reported, just descriptive results	High risk
Study Confounding	No control	High risk

*Perna, G., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	severe COPD participants that were on stable medications for 1 year; no current mood or anxiety disorders	Low risk
Study Attrition	No dropouts	Low risk
Outcome Measurement and Reporting	All pre-specified outcomes are reported.	Low risk
Study Confounding	No control	High risk

Riethmuller, J., et al.

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	Cystic fibrosis participants attending the CF center of the Children's University Hospital of Tuebingen; detailed inclusion and exclusion criteria	Low risk
Study Attrition	Even number of dropouts of treatment and placebo	Low risk
Outcome Measurement and Reporting	All pre-defined outcomes are reported	Low risk
Study Confounding	Randomized; Double-blinded	Low risk
Other	18 participants were analyzed with intent to treat (ITT), 13 were analyzed per protocol (PP). Authors report both ITT and PP results	Low risk

Series, F., et al.

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	COPD with and FEV <sub>1</sub> <65% and an FEV <sub>1</sub> /FVC <65%; clinical state and treatment unchanged for at least 4 weeks	Low risk
Study Attrition	Two participants were excluded before the second visit because the treatment for their COPD had been changed. Week 2 study not carried out in two participants because of technical problems, and one patient who developed bronchopneumonia was not evaluated at 10 weeks.	High risk
Outcome Measurement and Reporting	All pre-specified outcomes are reported.	Low risk
Study Confounding	No control	High risk
Other	The dose of protriptyline was reduced to 10 mg once a day after 2 weeks' treatment in two participants because of severe dryness of the mouth; pill counts	High risk

Series, F., et al. (1993)

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	Participants who were enrolled in previous trials	High risk
Study Attrition	The authors report a range of follow-up times, but say that on average it was equal for both the treatment and control groups	Low risk
Outcome Measurement and Reporting	All pre-specified outcome were reported	Low risk
Study Confounding	The treatment and control groups did not differ on their follow-up duration, age, weight, or pulmonary function.	Low risk
Other	Dose of protriptyline was reported as a range (10-20mg)	High risk

Strom, K., et al.

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	COPD with mild or moderate stable hypoxemia; detailed inclusion and exclusion criteria	Low risk
Study Attrition	Three participants receiving protriptyline were withdrawn from the trial, two because of side effects and one due to an exacerbation.	High risk
Outcome Measurement and Reporting	All pre-specified outcomes are reported.	Low risk
Study Confounding	Randomized study, method not described; Double-blind, placebo-controlled	Low risk
Other	No mention of patient compliance; baseline FEV <sub>1</sub> was different between treated and control groups although not significant	High risk

*Sugihara, H., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	Hospitalized in and out patients with bronchial asthma; no details given on inclusion and exclusion criteria	High risk
Study Attrition	No dropouts	Low risk
Outcome Measurement and Reporting	All pre-defined outcomes are reported	Low risk
Study Confounding	No control	High risk
Other	Participants who had wheezing, slight dyspnea only at night or severe drowsiness after use of Amitriptyline were given only single dose of 20-40mg at bedtime. If symptoms aggravated by drug, drug discontinued; if no response, the drug was increased until the patient showed a response one-way or the other. If no response seen after an appreciable length of time, therapy was discontinued.  Clinical evaluation was subjective. No statistical test were run	High risk

*Van Milligen., et al.*

<b>Domain</b>	<b>Description</b>	<b>Review author's judgment</b>
Study Participation	Persons with current depressive and/or anxiety disorders (n=1629) and healthy controls without lifetime diagnosis (n=629)	Low risk
Study Attrition	None	Low risk
Outcome Measurement and Reporting	All pre-specified outcomes are reported	Low risk
Study Confounding	Socio-demographic (age and years of education), health status (BMI, lung medication and chronic diseases) and lifestyle (smoking status and physical activity)	Low risk
Other	No control for severity of disease (depression)	High risk

Appendix Table 6. Demographic age, gender, and race/ethnicity breakdown from MESA Exam 1-5

Category		Exam 1	Exam 2	Exam 3	Exam 4	Exam 5
Age at Baseline	45-54	29%	29%	30%	30%	33%
	55-64	28%	28%	28%	28%	31%
	65-74	30%	29%	29%	30%	28%
	75-84	14%	14%	13%	12%	8%
Gender	Female	53%	52%	53%	53%	53%
	Male	47%	48%	47%	47%	47%
Race/Ethnicity	African-American	28%	27%	27%	27%	26%
	Chinese-American	12%	12%	12%	11%	12%
	Hispanic	22%	22%	21%	21%	21%
	White	39%	40%	40%	40%	39%
Total, n		6814	6239	5946	5818	4655

Appendix Table 7. MESA assay census for exams 1-5

	<b>Exam 1</b>	<b>Exam 2</b>	<b>Exam3</b>	<b>Exam4</b>	<b>Exam5</b>
	N=6814	N=6232	N=5939	N=5704	N=4651
Questionnaires					
Personal History	X	X	X	X	X
Medical History	X	X	X	X	X
Medications	X	X	X	X	X
Psycho-Social	X	X	X	X	X
Procedures/Assessments					
Anthropometry	X	X	X	X	X
Spirometry				A	A
X=MESA Classic cohort; A=Ancillary study					

Appendix Table 8. List of common medications that affect lung function

Aerobid	Monetelukast
Advair	Nasacort
Albuterol	Nasonex
Alupent	Primatene
Astelin	Pulmicort
Atrovent	Proventil
Azmacort	Pro Air
Brovana	Qvar
Bromotein	Rhinocort
Comivent	Serevent
Fluticasone	Singulair
Flonase	Spirivia
Flovent	Symbicort
Flunisolide	Theophylline
Formoterol	Veramyst
Intal	Ventolin
Ipratropium	Xopenex
Levalbuterol	

Appendix Table 9. Associations of confounders at exam 5 with selective serotonin reuptake inhibitors and outcome variables

Sample characteristics	Crude relationship to					
	OR	A. SSRI 95% CI	b	B. FEV1% 95% CI	OR	C. Dyspnea 95% CI
<b>Health Insurance</b>						
None	Ref	Ref	Ref	Ref	Ref	Ref
Medicaid	1.05	0.35 to 3.21	-1.86	-6.07 to 2.34	<b>1.75</b>	<b>0.97 to 3.14</b>
Medicare	1.38	0.50 to 3.84	-0.08	-4.07 to 3.91	1.27	0.71 to 2.27
HMO	1.54	0.62 to 3.84	-1.92	-5.38 to 1.53	<b>1.00</b>	<b>0.60 to 1.68</b>
VA/Other	<b>2.14</b>	<b>0.80 to 5.73</b>	2.04	-6.30 to 1.69	<b>1.59</b>	<b>0.90 to 2.80</b>
<b>Cigarette smoking status</b>						
Never-smokers	Ref	Ref	Ref	Ref	Ref	Ref
Former smokers	1.29	0.94 to 1.78	<b>-3.09</b>	<b>-4.58 to -1.59</b>	1.31	1.06 to 1.62
Current smokers	<b>2.02</b>	<b>1.42 to 3.41</b>	<b>-10.77</b>	<b>-13.73 to -7.82</b>	1.42	0.95 to 2.12
<b>Smoking pack-years</b>	<b>1.07</b>	<b>1.00 to 1.13</b>	<b>-1.65</b>	<b>-2.00 to -1.30</b>	<b>1.11</b>	<b>1.06 to 1.16</b>
<b>CES-D Score</b>	<b>1.06</b>	<b>1.04 to 1.07</b>	<b>-0.12</b>	<b>-0.21 to -0.02</b>	<b>1.06</b>	<b>1.05 to 1.07</b>

Bold indicates  $p < 0.20$  \*Smoking pack-years is per 10-years

Appendix Table 10. Unadjusted and adjusted difference-in-difference analysis of percent of predicted forced expiratory volume in one second: serotonin norepinephrine reuptake inhibitors

<b>Unadjusted</b>				
<b>Comparison group 1 n=28</b>	<b>SNRI use at Exam 4</b>	<b>SNRI use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	86%	85%	1	
Treatment Group (on/off)	96%	96%	0	
Difference	10	9	1	0.58
<b>Comparison group 2 n=2382</b>				
Control Group (off/off)	94%	96%	2	
Treatment Group (off/on)	92%	94%	2	
Difference	2	2	0	0.74
<b>Adjusted<sup>†</sup></b>				
<b>Comparison group 1 n=28</b>	<b>SNRI use at Exam 4</b>	<b>SNRI use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	105%	112%	7	
Treatment Group (on/off)	111%	116%	5	
Difference	6	4	2	0.74
<b>Comparison group 2 n=2382</b>				
Control Group (off/off)	93%	94%	1	
Treatment Group (off/on)	90%	92%	2	
Difference	3	2	1	0.59

The first comparison group had 19 patients that remained on serotonin norepinephrine reuptake inhibitors (control group) compared to 9 who went from being on serotonin norepinephrine reuptake inhibitors at exam 4 to being off them at exam 5 (treatment group). The second comparison group had 2356 patients that remained off serotonin norepinephrine reuptake inhibitors (control group) compared to 26 who went on them at exam 5 (treatment group).

<sup>†</sup>Adjusted for Centers for Epidemiologic Studies Depression Score, smoking status (never, former current) and smoking pack-years.

Appendix Table 11. Unadjusted and adjusted difference-in-difference analysis of percent of predicted forced expiratory volume in one second: tricyclic antidepressants

<b>Unadjusted</b>				
<b>Comparison group 1 n=29</b>	<b>TCA use at Exam 4</b>	<b>TCA use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	90%	93%	3	
Treatment Group (on/off)	99%	103%	4	
Difference	9	10	1	0.77
<b>Comparison group 2 n=2381</b>				
Control Group (off/off)	94%	96%	2	
Treatment Group (off/on)	87%	83%	4	
Difference	7	13	6	0.08
<b>Adjusted<sup>†</sup></b>				
<b>Comparison group 1 n=29</b>	<b>TCA use at Exam 4</b>	<b>TCA use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	80%	72%	8	
Treatment Group (on/off)	86%	76%	10	
Difference	6	4	2	0.57
<b>Comparison group 2 n=2381</b>				
Control Group (off/off)	93%	94%	1	
Treatment Group (off/on)	87%	83%	4	
Difference	6	11	5	0.11

The first comparison group had 13 patients that remained on tricyclic antidepressants (control group) compared to 16 who went from being on tricyclic antidepressants at exam 4 to being off them at exam 5 (treatment group). The second comparison group had 2366 patients that remained off tricyclic antidepressants (control group) compared to 15 who went on them at exam 5 (treatment group).

<sup>†</sup>Adjusted for Centers for Epidemiologic Studies Depression Score, smoking status (never, former current) and smoking pack-years.

Appendix Table 12. Unadjusted and adjusted difference-in-difference analysis of proportion of participants reporting dyspnea: serotonin norepinephrine reuptake inhibitors

<b>Unadjusted</b>				
<b>Comparison group 1 n=45</b>	<b>SNRI use at Exam 4</b>	<b>SNRI use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	25%	21%	4%	
Treatment Group (on/off)	25%	22%	3%	
Difference	0	1	1	0.96
<b>Comparison group 2 n=2365</b>				
Control Group (off/off)	13%	14%	1%	
Treatment Group (off/on)	16%	19%	3%	
Difference	3%	5%	2%	0.61
<b>Adjusted<sup>†</sup></b>				
<b>Comparison group 1 n=45</b>	<b>SNRI use at Exam 4</b>	<b>SNRI use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	25%	9%	16%	
Treatment Group (on/off)	19%	21%	2%	
Difference	6	12	18	0.17
<b>Comparison group 2 n=2365</b>				
Control Group (off/off)	13%	14%	1%	
Treatment Group (off/on)	5%	4%	1%	
Difference	8	10	2	0.84

The first comparison group had 19 patients that remained on serotonin norepinephrine reuptake inhibitors (control group) compared to 9 who went from being on serotonin norepinephrine reuptake inhibitors at exam 4 to being off them at exam 5 (treatment group). The second comparison group had 2356 patients that remained off serotonin norepinephrine reuptake inhibitors (control group) compared to 26 who went on them at exam 5 (treatment group).

<sup>†</sup>Adjusted for Centers for Epidemiologic Studies Depression Score, smoking status (never, former current) and smoking pack-years.

Appendix Table 13. Unadjusted and adjusted difference-in-difference analysis of proportion of participants reporting dyspnea: tricyclic antidepressants

<b>Unadjusted</b>				
<b>Comparison group 1 n=28</b>	<b>TCA use at Exam 4</b>	<b>TCA use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	39%	15%	24%	
Treatment Group (on/off)	20%	20%	0%	
Difference	19	5	24	0.23
<b>Comparison group 2 n=2382</b>				
Control Group (off/off)	13%	15%	2%	
Treatment Group (off/on)	38%	50%	12%	
Difference	25	35	10	0.23
<b>Adjusted<sup>†</sup></b>				
<b>Comparison group 1 n=28</b>	<b>TCA use at Exam 4</b>	<b>TCA use at Exam 5</b>	<b>Absolute difference between exam 4 and 5</b>	<b>p-value</b>
Control Group (on/on)	31%	7%	24%	
Treatment Group (on/off)	12%	14%	2%	
Difference	19	7	26	
<b>Comparison group 2 n=2382</b>				
Control Group (off/off)	13%	14%	1%	
Treatment Group (off/on)	33%	43%	10%	
Difference	20	29	9	0.38

The first comparison group had 13 patients that remained on tricyclic antidepressants (control group) compared to 16 who went from being on tricyclic antidepressants at exam 4 to being off them at exam 5 (treatment group). The second comparison group had 2366 patients that remained off tricyclic antidepressants (control group) compared to 15 who went on them at exam 5 (treatment group).

<sup>†</sup>Adjusted for Centers for Epidemiologic Studies Depression Score, smoking status (never, former, current) and smoking pack-years.

Appendix Table 14. Percent of predicted forced expiratory volume in one second at exam 4: controlling for depression only

	A. Unadjusted model		B. Adjusted model 1		C. Adjusted model 2	
	b	95% CI	b	95% CI	b	95% CI
<b>SSRI</b>	-4.66	-7.31 to -2.02	-4.27	-6.95 to -1.60	-4.41	-7.07 to -1.75
<b>CES-D Score (continuous)</b>			-0.07	-0.15 to 0.003		
<b>Depressed vs. not depressed</b>					-1.47	-3.20 to 0.26

Shaded variables or values were not included in the model.

Appendix Table 15. Percent of predicted forced expiratory volume in one second at exam 5: controlling for depression only

	A. Unadjusted model		B. Adjusted model		C. Adjusted model 2	
	b	95% CI	b	95% CI	b	95% CI
<b>SSRI</b>	-3.22	-6.37 to -0.08	-2.78	-5.96 to 0.39	-2.93	-6.10 to 0.23
<b>CES-D Score (continuous)</b>			-0.10	-0.20 to -0.010		
<b>Depressed vs. not depressed</b>					-1.73	-3.79 to 0.34

Shaded variables or values were not included in the model.

Appendix Table 16. Dyspnea at exam 4: controlling for depression only

	<b>A. Unadjusted model</b>		<b>B. Adjusted model</b>		<b>C. Adjusted model 2</b>	
	<b>OR</b>	<b>95% CI</b>	<b>OR</b>	<b>95% CI</b>	<b>OR</b>	<b>95% CI</b>
<b>SSRI</b>	1.99	1.41 to 2.80	1.38	0.96 to 1.99	1.63	1.15 to 2.32
<b>CES-D Score (continuous)</b>			1.07	1.06 to 1.08		
<b>Depressed vs. not depressed</b>					2.98	2.39 to 3.72

Shaded variables or values were not included in the model.

Appendix Table 17. Dyspnea at exam 5: controlling for depression only

	A. Unadjusted model		B. Adjusted model		C. Adjusted model 2	
	OR	95% CI	OR	95% CI	OR	95% CI
<b>SSRI</b>	1.76	1.20 to 2.57	1.39	0.93 to 2.06	1.50	1.01 to 2.21
<b>CES-D Score (continuous)</b>			1.06	1.05 to 1.07		
<b>Depressed vs. not depressed</b>					2.40	1.88 to 3.08

Shaded variables or values were not included in the model.

Appendix Table 18. SPIROMICS inclusion/exclusion criteria [112]

	No COPD		COPD	
	Non-smokers	Smokers	Mild/Mod COPD	Severe COPD
<b>Inclusion Criteria</b>				
Between age 40 and 80 (inclusive) at Baseline Visit	X	X	X	X
Able to tolerate and willing to undergo study procedures	X	X	X	X
<1 pack-year history of smoking	X			
>20 pack-year history of smoking		X	X	X
Pre-bronchodilator: FEV <sub>1</sub> /FVC $\geq$ .7 and FVC>LLN	X			
Post-bronchodilator: FEV <sub>1</sub> /FVC $\geq$ .7 and FVC>LLN		X		
Post bronchodilator: FEV <sub>1</sub> /FVC < .7 and FEV <sub>1</sub> > 50% pred			X	
Post bronchodilator: FEV <sub>1</sub> /FVC < .7 and FEV <sub>1</sub> < 50% pred				X
Able to understand English and/or Spanish	X	X	X	X
<b>Exclusion Criteria</b>				
Women only: Cannot be pregnant at baseline or plan to become pregnant during the course of the study	X	X	X	X
Dementia or other cognitive dysfunction which in the opinion of the investigator would prevent the participant from consenting to the study or completing study procedures	X	X	X	X
Has plans to leave the area in the next 3 years	X	X	X	X
Smoking history of > 1 pack-year but <21 pack-years	X	X	X	X
Has a BMI > 40 kg/m <sup>2</sup> at baseline exam	X	X	X	X
Prior significant difficulties with pulmonary function testing	X	X	X	X
Hypersensitivity to or intolerance of albuterol sulfate or ipratropium bromide or propellants or excipients of the inhalers	X	X	X	X
Non-COPD obstructive lung disease (various bronchiolitis, sarcoid, LAM, histiocytosis X) or parenchymal lung disease, pulmonary vascular disease, pleural disease, severe kyphoscoliosis, neuromuscular weakness, or other conditions, including clinically significant cardiovascular and pulmonary disease, that, in the opinion of the investigator, limit the interpretability of the pulmonary function measures.	X	X	X	X
History of interstitial lung disease	X	X	X	X
Current diagnosis of asthma	X			
History of lung volume reduction surgery or lung resection	X	X	X	X
History of lung or other organ transplant	X	X	X	X
History of endobronchial valve therapy	X	X	X	X
History of large thoracic metal implants (e.g., AICD and/or pacemaker) that in the opinion of the investigator limit the interpretability of CT scans	X	X	X	X
Currently taking $\geq$ 10mg a day/20mg every other day of prednisone or equivalent systemic corticosteroid	X	X	X	X
Currently taking any immunosuppressive agent	X	X	X	X
Current illicit substance abuse, excluding marijuana	X	X	X	X
History of or current use of IV Ritalin	X	X	X	X
History of or current use of heroin	X	X	X	X
History of illegal IV drug use within the last 10 years or more than 5 instances of illegal IV drug use ever	X	X	X	X
Known HIV/AIDS infection	X	X	X	X
History of lung cancer or any cancer that spread to multiple locations in the body	X	X	X	X
History of or current exposure to chemotherapy or radiation treatments that, in the opinion of the investigator, limits the interpretability of the pulmonary function measures.	X	X	X	X
Diagnosis of unstable cardiovascular disease including myocardial infarction in the past 6 weeks, uncontrolled congestive heart failure, or uncontrolled arrhythmia	X	X	X	X

Appendix Table 19. Baseline characteristics by antidepressant medication use

Sample characteristics	No anti- Depressant N=1827	SSRI N=321	SNRI N=34	TCA N=48
	N and (%) or Mean±SD	N and (%) or Mean±SD	N and (%) or Mean±SD	N and (%) or Mean±SD
Age, years, mean±SD	64±9	64±9	59±8	65±8
<b>Gender</b>				
Male	1017 (56)	113 (35)	12 (35)	18 (38)
Female	810 (44)	208 (65)	22 (65)	30 (63)
<b>Race</b>				
White	1422 (78)	280 (87)	28 (82)	40 (83)
Black	326 (18)	27 (8)	4 (12)	4 (8)
Asian	21 (1)	1 (.31)	1 (3)	0 (0)
Pacific Islander	41 (2)	7 (2)	0 (0)	2 (4)
American Indian	7 (.38)	2 (.62)	0 (0)	1 (2)
Mixed	10 (.55)	4 (1)	1 (3)	1 (2)
Height, cm, mean±SD	170±10	168±9	165±10	167±8
Weight, kg, mean±SD	82±18	81±18	78±19	82±18
<b>Current or former smokers</b>				
Yes	618 (34)	113 (35)	15 (44)	16 (33)
No	1209 (66)	208 (65)	19 (56)	32 (67)
Smoking history pack-years#	48±41	49±29	41±21	53±30
FEV <sub>1</sub> % predicted, mean±SD	67±27	66±28	71±29	74±24
<b>COPD Stage</b>				
None	526 (31)	107 (34)	13 (39)	18 (38)
Mild	284 (17)	33 (11)	3 (9)	8 (17)
Moderate	530 (31)	94 (30)	10 (30)	16 (33)
Severe	262 (15)	58 (19)	7 (21)	6 (13)
Very Severe	117 (7)	21 (7)	0 (0)	0 (0)
<b>HADS Score, mean±SD</b>				
Depressed (HADS≥8)	4±3 276 (15)	6±4 92 (29)	8±4 16 (47)	5±4 12 (25)
<b>Number of exacerbations prior to enrolling</b>	0.30±0.70	0.52±1.00	0.62±1.07	0.33±1.00

cm: centimeters, kg: kilogram; FEV<sub>1</sub>: forced expiratory volume in one second; HADS: Hospital Anxiety and Depression scale; SSRI: selective serotonin reuptake inhibitors, TCA: tricyclic antidepressants, SNRI: serotonin-norepinephrine reuptake inhibitors; #among ever-smokers.

Appendix Table 20. Crude and adjusted Hazard Ratios (HRs) for time to first exacerbation using time dependent cox regression: serotonin norepinephrine reuptake inhibitors

	A. Unadjusted model		B. SNRIs and Depression		C. Adjusted model <sup>†</sup>	
	b	95% CI	b	95% CI	b	95% CI
<b>SNRI vs. Other*</b>	1.27	0.75 to 2.15	0.96	0.56 to 1.63	1.18	0.60 to 2.31
<b>Depression score</b>			1.09	1.07 to 1.11	1.04	1.01 to 1.07
<b>Age<sup>‡</sup></b>					0.97	0.85 to 1.10
<b>Gender</b>					1.43	1.18 to 1.74
<b>Baseline FEV1<sup>‡</sup></b>					0.82	0.78 to 0.85
<b>Prior Exacerbations</b>					1.41	1.31 to 1.52
<b>Current Smoker</b>					0.94	0.75 to 1.17
<b>Pack-years<sup>‡</sup></b>					1.01	0.99 to 1.03

\*Other indicates participants that were on other antidepressants or on no antidepressants. †Time-dependent variables included antidepressant status, current smoking status, smoking pack-years, and HADS depression score. ‡Age, baseline FEV1, and pack-years are all divided by 10.

Appendix Table 21. Crude and adjusted Hazard Ratios (HRs) for time to first exacerbation using time dependent cox regression: tricyclic antidepressants

	A. Unadjusted model		B. TCAs and Depression		C. Adjusted model <sup>†</sup>	
	b	95% CI	b	95% CI	b	95% CI
<b>TCA vs. Other*</b>	1.28	0.79 to 2.07	1.15	0.71 to 1.86	1.50	0.77 to 2.91
<b>Depression score</b>			1.09	1.07 to 1.11	1.04	1.01 to 1.07
<b>Age<sup>‡</sup></b>					0.97	0.85 to 1.10
<b>Gender</b>					1.43	1.17 to 1.74
<b>Baseline FEV1<sup>‡</sup></b>					0.82	0.78 to 0.85
<b>Prior Exacerbations</b>					1.41	1.32 to 1.52
<b>Current Smoker</b>					0.95	0.76 to 1.18
<b>Pack-years<sup>‡</sup></b>					1.01	0.99 to 1.03

\*Other indicates participants that were on other antidepressants or on no antidepressants. †Time-dependent variables included antidepressant status, current smoking status, smoking pack-years, and HADS depression score. ‡Age, baseline FEV1, and pack-years are all divided by 10.

Appendix Table 22. Crude and adjusted Hazard Ratios (HRs) for time to first exacerbation using time dependent cox regression: any antidepressants

	A. Unadjusted model		B. TCAs and Depression		C. Adjusted model <sup>†</sup>	
	b	95% CI	b	95% CI	b	95% CI
<b>Any vs. Other*</b>	1.38	1.56 to 1.64	1.17	0.98 to 1.40	1.18	0.93 to 1.50
<b>Depression score</b>			1.08	1.06 to 1.10	1.04	1.01 to 1.07
<b>Age<sup>‡</sup></b>					0.97	0.85 to 1.10
<b>Gender</b>					1.41	1.15 to 1.72
<b>Baseline FEV1<sup>‡</sup></b>					0.82	0.78 to 0.85
<b>Prior Exacerbations</b>					1.41	1.32 to 1.52
<b>Current Smoker</b>					0.94	0.76 to 1.18
<b>Pack-years<sup>‡</sup></b>					1.01	0.99 to 1.03

\*Other indicates participants that were on other antidepressants or on no antidepressants. <sup>†</sup>Time-dependent variables included antidepressant status, current smoking status, smoking pack-years, and HADS depression score. <sup>‡</sup>Age, baseline FEV1, and pack-years are all divided by 10.

Appendix Table 23. Crude and adjusted Hazard Ratios (HRs) for time to first exacerbation using time dependent cox regression: Depressed

	A. Unadjusted model		B. SSRIs and Depression		C. Adjusted model <sup>†</sup>	
	b	95% CI	b	95% CI	b	95% CI
<b>SSRI vs. Other*</b>	0.96	0.67 to 1.37	0.93	0.65 to 1.34	0.89	0.56 to 1.39
<b>Depression score</b>			1.03	0.98 to 1.08	1.03	0.94 to 1.12
<b>Age<sup>‡</sup></b>					0.93	0.71 to 1.21
<b>Gender</b>					1.51	1.00 to 2.30
<b>Baseline FEV1<sup>‡</sup></b>					0.86	0.79 to 0.93
<b>Prior Exacerbations</b>					1.35	1.19 to 1.53
<b>Current Smoker</b>					0.96	0.64 to 1.46
<b>Pack-years<sup>‡</sup></b>					0.94	0.86 to 1.03

\*Other indicates participants that were on other antidepressants or on no antidepressants. <sup>†</sup>Adjusted for age, gender, smoking status, pack-years, HADS depression score, baseline FEV1 and prior number of exacerbations before enrolling into the study. Time-dependent variables included antidepressant status, current smoking status, smoking pack-years, and HADS depression score. <sup>‡</sup>Age, baseline FEV1, and pack-years are all divided by 10.

Appendix Table 24. Crude and adjusted Hazard Ratios (HRs) for time to first exacerbation using time dependent cox regression: Not depressed

	A. Unadjusted model		B. SSRIs and Depression		C. Adjusted model <sup>†</sup>	
	b	95% CI	b	95% CI	b	95% CI
<b>SSRI vs. Other*</b>	1.43	1.14 to 1.79	1.32	1.05 to 1.65	1.27	0.93 to 1.73
<b>Depression score</b>			1.11	1.07 to 1.14	1.09	1.03 to 1.15
<b>Age<sup>‡</sup></b>					0.99	0.86 to 1.14
<b>Gender</b>					1.42	1.13 to 1.78
<b>Baseline FEV1<sup>‡</sup></b>					0.81	0.77 to 0.84
<b>Prior Exacerbations</b>					1.47	1.35 to 1.61
<b>Current Smoker</b>					0.92	0.71 to 1.20
<b>Pack-years<sup>‡</sup></b>					1.02	1.00 to 1.03

\*Other indicates participants that were on other antidepressants or on no antidepressants. <sup>†</sup>Adjusted for age, gender, smoking status, pack-years, HADS depression score, baseline FEV1 and prior number of exacerbations before enrolling into the study. Time-dependent variables included antidepressant status, current smoking status, smoking pack-years, and HADS depression score. <sup>‡</sup>Age, baseline FEV1, and pack-years are all divided by 10.

Appendix Table 25. Generalized linear regression coefficients for Baron and Kenny mediation steps for Interleukin-6 receptor as a mediator of the relationship between selective serotonin reuptake inhibitors and forced expiratory volume in one second excluding participants without COPD

	A. SSRI to FEV1*		B. SSRI to IL6		C. IL6 to FEV1		D. SSRI to FEV1 controlling for IL6*	
	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Visit 1	-2.88	-7.53 to 1.77	0.006	-0.02 to 0.03	0.12	-0.06 to 0.30	-3.01	-7.66 to 1.64
Visit 2	-0.76	-10.14 to 8.61	-0.03	-0.07 to 0.006	-0.02	-0.04 to 0.32	-0.79	-10.20 to 8.63

SSRI: selective serotonin reuptake inhibitor; FEV1: forced expiratory volume in one second

\*additionally controlled for HADS depression score since this was a significant confounder between SSRI and FEV1

Appendix Table 26. Generalized linear regression coefficients for Baron and Kenny mediation steps for C-reactive protein as a mediator of the relationship between selective serotonin reuptake inhibitors and forced expiratory volume in one second excluding participants without COPD

	A. SSRI to FEV1*		B. SSRI to CRP		C. CRP to FEV1		D. SSRI to FEV1 controlling for CRP*	
	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Visit 1	-2.88	-7.53 to 1.77	-0.003	-0.15 to 0.15	-3.85	-5.11 to -2.58	-3.16	-7.75 to 1.44
Visit 2	-0.76	-10.14 to 8.61	0.03	-0.23 to 0.30	-5.00	-7.29 to -2.71	-1.42	-10.57 to 7.74

SSRI: selective serotonin reuptake inhibitor; FEV1: forced expiratory volume in one second

\*additionally controlled for HADS depression score since this was a significant confounder between SSRI and FEV1

## STATISTICAL APPENDIX

### HANDLING MISSING DATA

For Chapter 3 and Chapter 4, we employed the complete case method for missing data, which involves the analysis of the set of observations with no missing values. When missing data is Missing Completely at Random (MCAR), this estimator is unbiased.

In Chapter 3, we only had 664 observations that were dropped due to missing values; therefore, this method was logical to employ in a large dataset, minimizing the efficiency losses. To assess any potential biases from removing incomplete cases, we compare the missing and non-missing observations on available data [132]. We compared the demographics of the participants with missing variables (Appendix Table 27 *Error! Reference source not found.* and Appendix Table 28). At exam 4, 295 participants were missing information on medications, 112 on spirometry, 216 on dyspnea, 231 on CES-D score, 187 on health insurance and smoking status, and 184 on smoking pack-years; this led to a total of 664 participants being excluded. In those with missing information, there was a higher proportion of males, Asians, Hispanics, and mild COPD. Although statistically significant, this is likely due to the large sample size. At exam 5, 98 participants were missing information on medications, 23 on spirometry, 202 on dyspnea, 200 on CES-D score, 131 on health insurance, 146 on smoking status, and 184 on smoking pack-years; this led to a total of 406 participants being excluded. Similar to exam 4, in those with missing information, there was a higher proportion of males and Asians. Additionally, there was also a larger proportion of those with no COPD and a smaller proportion of people reporting dyspnea.

In Chapter 4, there were 97 participants missing information on demographics (age, gender), 146 missing HADS depression score, 102 missing FEV1, 723 missing antidepressant medication use, 139 missing smoking status, and 198 with no exacerbation follow-up information, leading to 853 participants being excluded (

Appendix Table 29). In those with missing information, there was a higher proportion of Black participants, current smokers, and participants with no COPD. Although statistically significant, this is likely due to the large sample size; there were no clinically meaningful differences between the missing and non-missing cohorts that would suggest that our results would be different with the inclusion of these participants, had they had complete data.

Appendix Table 27. MESA: Basic demographic comparison of missing and non-missing observations:  
Exam 4

Sample characteristics	Missing N=664		Not Missing N=3542		p-value
	N or mean±SD	%	N or mean±SD	%	
<b>Age, years</b>	67±10	na	66±10	na	<0.001
<b>Gender</b>					
<b>Male</b>	266	48	1748	49	0.51
<b>Female</b>	290	52	1794	51	
<b>Race/ethnicity</b>					
<b>White</b>	253	46	1254	35	<0.001
<b>Asian</b>	39	7	567	16	
<b>African-American</b>	195	35	907	26	
<b>Hispanic</b>	69	12	814	23	
<b>Height, cm</b>	167±10	na	166±10	na	0.05
<b>BMI, kg/m<sup>2</sup></b>	29±6	na	28±6	na	0.03
<b>Health Insurance</b>					
<b>None</b>	18	4	189	5	0.04
<b>Medicaid</b>	28	6	297	8	
<b>Medicare</b>	58	12	341	10	
<b>HMO</b>	310	65	2331	66	
<b>VA/Other</b>	63	13	384	11	
<b>Cigarette smoking status</b>					
<b>Never-smokers</b>	209	44	1835	52	0.03
<b>Former smokers</b>	210	44	1371	39	
<b>Current smokers</b>	57	12	325	9	
<b>Smoking history pack-years<sup>#</sup></b>	24±23	na	22±26	na	0.32
<b>FEV<sub>1</sub> % predicted, mean (SD)</b>	91±19	na	94±18	na	0.02
<b>COPD Stage</b>					
<b>None</b>	277	79	2757	78	0.003
<b>Mild</b>	30	9	449	13	
<b>Moderate</b>	33	10	295	8	
<b>Severe</b>	8	2	35	1	
<b>Very Severe</b>	3	1	6	<1	
<b>Dyspnea, No. (%)</b>	84	19	541	15	0.06
<b>CES-D Score</b>					
<b>Depressed (CES-D≥16)</b>	70	11	489	14	0.02

\*Among ever smokers

Appendix Table 28. MESA: Basic demographic comparison of missing and non-missing observations:  
Exam 5

Sample characteristics	Missing N=406		Not Missing N=2954		p-value
	N or mean±SD	%	N or mean±SD	%	
<b>Age, years</b>	73±10	na	69±9	na	<0.001
<b>Gender</b>					
<b>Male</b>	178	53	1449	49	0.42
<b>Female</b>	156	47	1505	51	
<b>Race/ethnicity</b>					
<b>White</b>	131	39	1134	38	0.003
<b>Asian</b>	25	8	424	14	
<b>African-American</b>	104	31	763	26	
<b>Hispanic</b>	74	22	633	21	
<b>Height, cm</b>	165±10	na	166±10	na	0.03
<b>BMI, kg/m<sup>2</sup></b>	29±6	na	28±6	na	0.003
<b>Health Insurance</b>					
<b>None</b>	12	5	136	5	0.03
<b>Medicaid</b>	27	10	233	8	
<b>Medicare</b>	42	16	320	11	
<b>HMO</b>	150	57	1944	66	
<b>VA/Other</b>	33	13	318	11	
<b>Cigarette smoking status</b>					
<b>Never-smokers</b>	130	50	1595	54	0.42
<b>Former smokers</b>	108	42	1146	39	
<b>Current smokers</b>	20	8	191	7	
<b>Smoking history pack-years<sup>#</sup></b>	24±25	na	22±25	na	0.12
<b>FEV<sub>1</sub> % predicted, mean (SD)</b>	96±42	na	95±20	na	0.66
<b>COPD Stage</b>					
<b>None</b>	172	63	2169	74	<0.001
<b>Mild</b>	36	13	457	16	
<b>Moderate</b>	13	12	275	9	
<b>Severe</b>	12	4	47	2	
<b>Very Severe</b>	19	7	2	<1	
<b>Dyspnea, No. (%)</b>	36	18	440	15	0.29
<b>CES-D Score</b>	8±7	na	8±8	na	0.38
<b>Depressed (CES-D≥16)</b>	32	8	421	14	<0.001

\*Among ever smokers

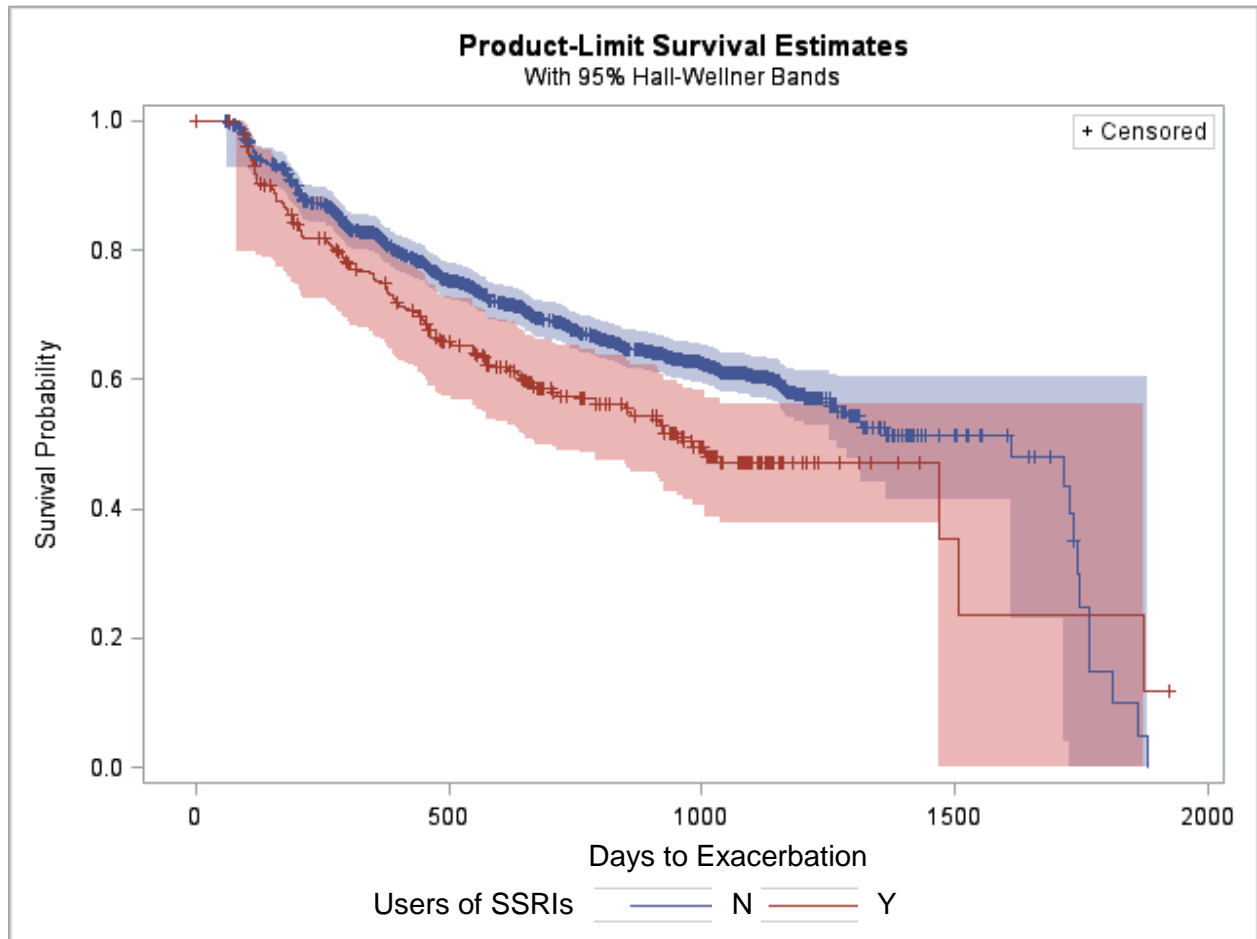
Appendix Table 29. SPIROMICS: Basic demographic comparison of missing and non-missing observations

Sample characteristics	Missing N=853		Not Missing N=2221		p-value
	N or mean±SD	%	N or mean±SD	%	
Age, years	59±10		64±9		<0.001
Gender					
Male	420	56	1158	52	0.10
Female	336	44	1063	48	
Race/ethnicity					
White	505	67	1761	79	<0.001
Black	215	28	361	16	
Asian	10	1	23	1	
American Indian	4	.53	10	.45	
Pacific Islander	1	.13	0	0	
Mixed	18	2	51	2	
Height, cm	170±9		170±10		0.18
Weight, kg	79±18		81±18		0.001
Current smokers					
Yes	334	47	760	34	<0.001
No	380	53	1461	66	
Smoking history pack-years <sup>#</sup>	41±30		48±39		<0.001
FEV <sub>1</sub> % predicted	71±28		67±27		0.002
COPD Stage					
None	263	39	661	31	<0.001
Mild	77	12	327	16	
Moderate	176	26	647	31	
Severe	103	15	331	16	
Very Severe	48	7	138	7	
HADS Score	4±4		4±3		0.26
Depressed (HADS≥8)	127	15	294	18	0.06
Number of exacerbations prior to enrolling	0.44±1.00		0.41±0.89		0.42

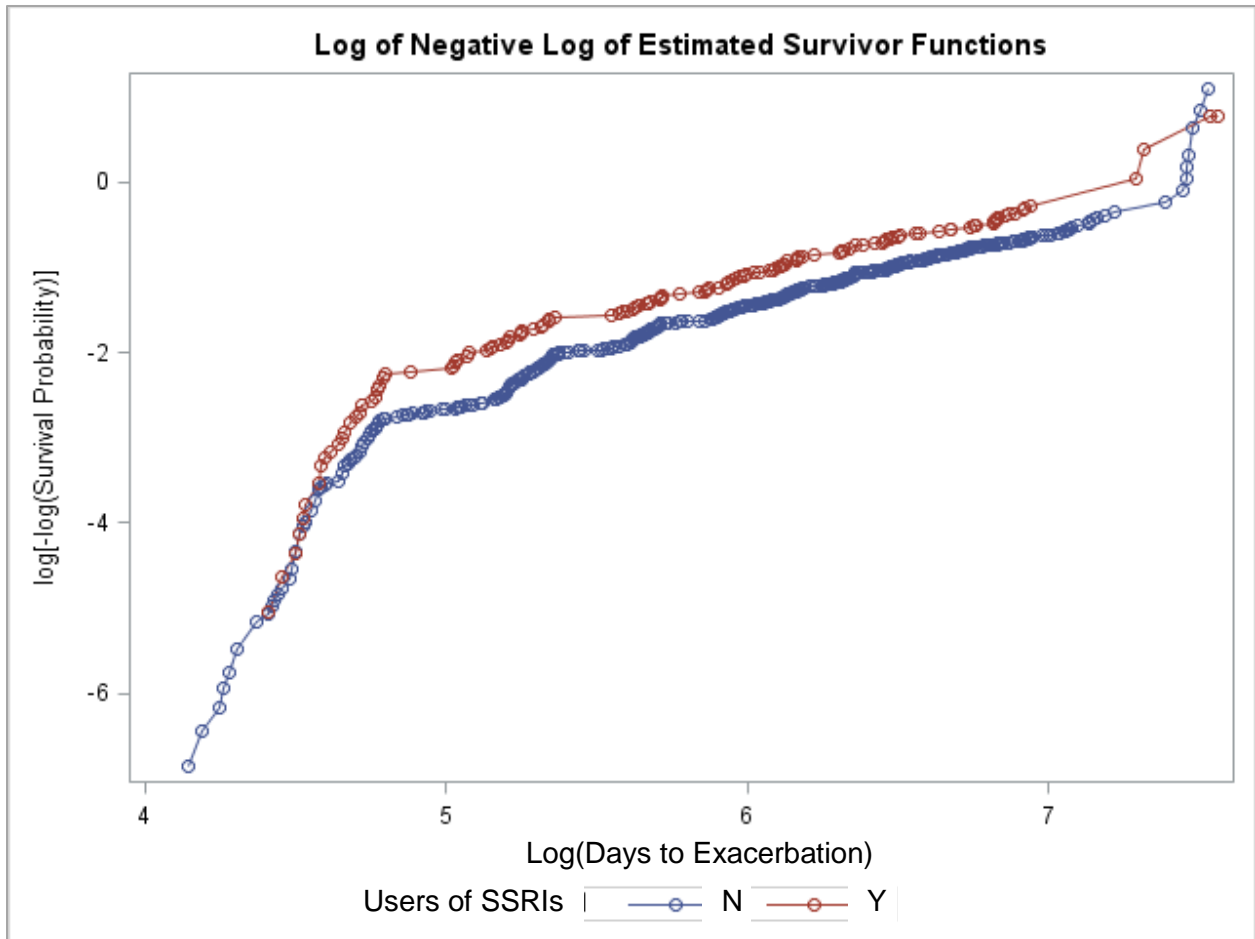
\*Among ever smokers

## ASSESSING PROPORTIONAL HAZARDS

A graph of the Kaplan-Meier estimate of the survival function was created to check for proportional hazards. As seen below, the survival function is approximately parallel, does not cross until the data are sparse near the end of follow-up and slowly diverges throughout time.



The log-log plot plots the logarithm of the negative logarithm of the estimated survivor function against the logarithm of survival time. The curves are parallel in the plot below, indicating proportional hazards across groups.



In order to check the linearity of the covariate vector, the Schoenfeld Residuals against time were examined. There is no increasing pattern, until the end where observations become sparse.

