Original Research

Exacerbations and Decreased Lung Function Predict Nebulizer Use and Uptake in COPD and Tobacco Exposed Persons With Preserved Spirometry

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Abstract

Rationale: Nebulizers are an alternative to handheld devices for inhaled therapies in chronic obstructive pulmonary disease (COPD). Understanding nebulizer utilization patterns is essential to developing therapy guidelines.

Objectives: To describe characteristics of nebulizer users versus nonusers and factors associated with baseline nebulizer use and longitudinal uptake.

Methods: We analyzed SPIROMICS, a prospective cohort of 2,973 participants with or without tobacco use and/or COPD. We used cross-sectional multivariable logistic regression and interval-censored proportional hazard models to analyze factors associated with nebulizer use and uptake among tobacco-exposed participants with preserved spirometry (TEPS) and COPD from enrollment (Visit 1) through 4-7 years of follow-up (Visit 5).

Results: Nebulizer utilization was highest in advanced COPD, 49% of GOLD D participants at baseline. Nebulizer treatments were primarily as-needed short-acting bronchodilators. Baseline nebulizer use was associated with respiratory exacerbations in the prior year (one, OR 1.81, 95%CI [1.24,2.64]; two, OR 1.86, 95%CI [1.07,3.22]; three or more, OR 1.87, 95% CI [1.07,3.28]), lower FEV_1 (OR 2.81 per Liter decrease, 95% CI [2.09, 3.77]), CAT score > 10 (OR 1.89, 95% CI [1.17, 3.03]), 6MWD distance (OR 1.03 per 10 meter lower 6MWD, 95% CI [1.02,1.05]), and a history of asthma (OR 2.41, 95%CI [1.76,3.30]). Longitudinal uptake was similarly associated with exacerbations, lower FEV_1, CAT > 10, and asthma. Patterns were consistent between TEPS and COPD.

Conclusion: Nebulizers were predominantly used by participants with frequent exacerbations, high symptom burden and advanced COPD, and long-acting nebulized medications were underutilized. Randomized controlled trials are needed compare nebulizers with hand-held devices.

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Introduction

Inhaled pharmacotherapies are the staple of symptom management in chronic obstructive pulmonary disease (COPD) because they deliver a high concentration of drug directly to the lungs, reducing systemic side effects.[1,2] The mainstay of inhaled treatments in COPD includes bronchodilators such as muscarinic antagonists, beta-sympathomimetic agonists, and inhaled corticosteroids (ICS) for patients experiencing exacerbations and eosinophilia.[3] These medications are delivered via either hand-held inhaler devices such as pressurized-metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), soft-mist inhalers (SMIs), or via nebulizers.[4]

Nearly two-thirds of COPD patients use nebulizers at some point;[5] however, patterns and guidelines for nebulizer prescribing have not been adequately developed.[6,7] Furthermore, a third of inhaler users demonstrate poor technique, with coordination, speed/depth of inhalation, and failure to fully exhale before inhalation or a post-inhalation breath hold as the most common errors.[8–11] Additional predictors of ineffective handheld inhaler use include older age, lower levels of education and socio-economic status, prescription of multiple devices, and inadequate peak inspiratory flow.[6,12–14] Studies link incorrect inhaler technique to worse health-related quality of life and increased exacerbations in Asthma and COPD.[6] Nebulized delivery is a practical alternative for patients with poor respiratory effort, cognitive impairment, or impaired dexterity.[15]

Small observational studies have associated hypoxemia, increased exacerbation frequency and worsening health status, as indicated by higher COPD Assessment Test [CAT] scores with nebulizer use.[5] Additionally, many tobacco-exposed persons with preserved spirometry (TEPS) report significant respiratory symptom burden, exacerbations, and have potential for disease progression.[16,17] A randomized controlled trial of handheld bronchodilators among TEPS did not show benefit.[18] However, randomized or longitudinal cohort studies have not evaluated nebulizer

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utilization in TEPS, which prompted their inclusion in our analysis. Additionally, assessment of the effectiveness of nebulizers versus handheld delivery devices are sparse in COPD and TEPS,[19,20] yet observational studies suggest potential benefits in quality of life and symptom management in COPD with nebulized delivery.[21,22] However, little is known about patterns of nebulizer uptake and utilization in relationship to clinical and epidemiologic features of patients with COPD.

Using a longitudinal cohort of individuals with spirometry-proven COPD and tobacco-exposed persons with preserved spirometry (TEPS), we sought to understand the patterns of nebulizer use and identify and quantify factors associated with nebulizer uptake. We hypothesized that recent exacerbations, greater symptom burden, and more severe obstructive ventilatory defects independently predict baseline utilization and longitudinal uptake of nebulizers among TEPS and those with COPD. Although not a primary or secondary SPIROMICS objective, this analysis leverages rich longitudinal data to examine factors associated with nebulizer use among persons with and at risk for COPD, an area with limited prior longitudinal study.

Methods:

Study Population

SPIROMICS (the Sub-Populations and Intermediate Outcome Measures in COPD Study) is a multicenter prospective cohort study that enrolled TEPS, tobacco-exposed persons with COPD, and non-smoking controls across 12 US institutions.[23] This analysis was conducted post-hoc using data collected prospectively. Participants completed in-person physiologic and laboratory assessments at four approximately annual in-person visits (V1-V4) and a 5th visit (V5) 4.2 ± 0.8 years (mean ± SD) after V4. We analyzed data from V1 to V5 from years 2012 to 2021. We restricted this analysis to participants with tobacco exposure (≥20 pack years) with or without

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COPD at study entry and without missing data on baseline nebulizer use (Figure 1). The research protocol for SPIROMICS was approved by the institutional review board of all participating institutions, and written informed consent was obtained from all participants.

Outcome and Variable Definitions

We categorized participants into two outcome groups by baseline nebulizer use (yes/no). Nebulizer use was self-reported as any use of nebulizers within the last 3 months prior to study V1 through V4 (yes/no). At V5 the data collection instrument was changed to ask "do you regularly use nebulizers?," (yes/no) and if affirmative, frequency of use was collected (daily/as needed) (yes/no) (Supplemental Figure 1). The V5 questionnaire also surveyed nebulized drug type, which was limited to approved drugs at the time of survey development.

We evaluated the following self-reported sociodemographic characteristics: age, sex, racial/ethnicity identity, household income, and tabulated Area Deprivation Index (ADI). The ADI is a neighborhood-level variable obtained by geocoding participants' addresses to US Census block groups and then matching them to the neighborhood-level ADI percentile, a composite measure of neighborhood disadvantage ranging from 1-100 (higher indicating more disadvantaged). ADI has been associated with worse outcomes in COPD patients.[24,25,26]

We assessed the following clinical features: body mass index, smoking status (current/former), history of asthma (yes/no), chronic bronchitis (yes/no, based on responses to the St. George's Respiratory Questionnaire, SGRQ),[27] post-bronchodilator forced expiratory volume in 1 second (FEV_1),[28] presence of COPD (defined by post-bronchodilator $FEV_1/FVC < 0.70$), and post-bronchodilator inspiratory capacity (IC) derived from the slow vital capacity.

Exercise capacity was measured based on the six-minute walk distance (6MWD)[29] and the Veterans Specific Activity Questionnaire (VSAQ) (1-13, higher scores indicating greater self-

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reported exercise capacity).[30] Respiratory symptom burden was assessed using: CAT score (0-40),[31] modified Medical Research Council (mMRC) dyspnea score (0-4) with higher scores indicating greater symptom burden,[32] and frequency of moderate to severe exacerbations (prescribed antibiotics or corticosteroids) in the 12 months preceding enrollment and between visit intervals. Respiratory-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ).[33] All data were collected at V1-V5, except exacerbationswere reported during quarterly phone calls between each visit.

Statistical Analysis

To assess differences in sociodemographic and clinical characteristics between nebulizer use groups at baseline, we first performed a cross-sectional analysis at V1. Continuous variables were compared using the Wilcoxon rank-sum test and categorical variables were compared using Pearson's chi-squared test. We then examined the type of nebulized medications used between mutually exclusive categories of daily maintenance versus as-needed use (data only available for V5), using Fisher's exact test due to low cell counts.

We tested associations between participant factors and baseline nebulizer use with a cross-sectional multivariable logistic regression comparing baseline nebulizer users to non-users, controlling for age, sex, race, ADI, BMI, COPD diagnosis at study entry, enrollment smoking status, history of asthma, chronic bronchitis, absolute FEV_1 (Liters), number of exacerbations during the year prior to enrollment, CAT score, and 6MWD (meters). We used a conceptual framework based on existing literature to determine the above listed covariates of interest, and further refined the model using tests of collinearity.

To evaluate factors associated with the uptake of nebulizers during the study period, we performed a longitudinal subgroup analysis of all those who did not use nebulizers at or within 3

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months of baseline. We compared those who initiated nebulizer use during the study following V1 to those who never used nebulizers using time-to-event analysis via an interval-censored proportional hazards (ICPH) model controlling for the same covariates analyzed in the baseline logistic regression model, detailed above.[34,35] Because event times were interval-censored, primary time-to-event analyses were conducted using ICPH models. Kaplan-Meier curves were included for descriptive visualization and were constructed by assigning events to the visit date at which they were first observed. These curves do not account for interval censoring and should be interpreted as approximate summaries of observed event patterns rather than formal survival estimates. Time invariant variables included race, ADI, income, COPD status, and history of asthma. Time-varying variables included current smoking status, chronic bronchitis using SGRQ criteria, CAT score, FEV_1, six-minute walk distance, and exacerbation frequency. Due to collinearity, age was modeled as time-invariant using V1 age rather than time-varying. The outcome of interest was time to initiation of nebulizer use at a subsequent visit. Subgroup analyses were also independently performed on the TEPS and COPD groups.

All analyses were completed using Stata version 18.0 (College Station, TX) using a two-tailed alpha of 0.05. Missing values for ADI were imputed using the mean ADI for that study site and accounted for 2.9% of the data. Complete case analysis was used for all statistical models.

Results:

Characteristics of Participants at Study Enrollment

Of the 2,147 participants included in the baseline cross-sectional analysis (Figure 1), 33.3%(717) were TEPS and 66.6%(1,430) had COPD. At baseline, 12%(265) reported nebulizer use (5% of TEPS [35/717] compared to 16.1% of COPD participants [230/1,430] (Supplemental

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Table 1). Nearly half of those in both GOLD Stage 4 (42%,[48/115]) and formerly GOLD Group D (49%,[56/115]) (noting that a subsequent guideline change collapsed groups C and D into group E) reported nebulizer use at baseline. Nebulizer users were slightly younger and more often female (Table 1). Nebulizer users also had significantly higher rates of overall neighborhood level disadvantage by ADI (45.2±28.7 vs.36.8 ±27.7 percentile, mean±SD, P<0.001)]. Additionally, household incomes were more often <$15,000 among nebulizer users (31%[81/265]vs. 18%[332/1,882], P<0.001). Nebulizer users were also more likely to identify as Black (27% vs. 17%, P<0.001).

Nebulizer users more often reported a diagnosis of COPD (87%[230/265] vs 64%1,200/1,882], P<0.001) or asthma (43%[114/265] vs. 18%[333/1,882], P <0.001) at baseline compared to non-users. They also more frequently had chronic bronchitis (60%[158/265] vs. 42%[792/1,882], P<0.001), but the groups did not differ in current smoking status. Baseline pulmonary function was lower among nebulizer users (Table 1), both by post-bronchodilator FEV_1 (1.4±0.7L vs. 2.1±0.9L, P<0.001) and inspiratory capacity (IC, 2.2±0.8L versus 2.7±0.8L, P<0.001). More severe symptoms by CAT and SGRQ and poorer exercise capacity by VSAQ and 6MWD were seen among nebulizer users (Table 1). Nebulizer users were also more likely to have more frequent exacerbations within the year before enrollment, (one, 23%[62/265] vs. 11%[198/1,882]; two, 10%[27/265] versus 3%[69/1,882]; or three or more, 11%[29/265] versus 3%[55/1,882] compared to no exacerbations; P<0.001).

Among TEPS who used nebulizers, most were symptomatic by CAT, SGRQ and MMRC, 60%[21/35] had a history of asthma and 77%[27/35] and chronic bronchitis.Apart from lung function measures, characteristics of nebulizer users among participants with COPD and TEPS were similar (Supplemental Table 1).

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Prediction of Nebulizer Use at Study Enrollment

In the cross-sectional multivariable logistic regression analysis (Table 2 for both bivariate and adjusted estimates), significant factors associated with baseline nebulizer use included history of asthma (OR 2.41, 95%CI[1.76,3.30]), more moderate/severe COPD exacerbations within the last year (one, OR 1.81, 95%CI[1.24,2.64]; two, OR 1.86, 95%CI[1.07,3.22]; three or more, OR 1.87, 95%CI[1.07,3.28]), FEV_1 absolute (OR 2.81 per Liter lower baseline FEV_1, 95%CI[2.09,3.77]), CAT score ≥ 10 (OR 1.89, 95%CI[1.17,3.03]), 6MWD distance (OR 1.03 per 10 meters lesser baseline 6MWD, 95%CI[1.02,1.05]). These findings were robust to sensitivity analysis, with few covariates changing sign or statistical significance, and none had both a sign and significance change (Supplemental Table 2). SGRQ, VSAQ, and IC were all dropped from the model due to collinearity with CAT or FEV_1 (pearson correlation coefficient > 0.7, P<0.001).

Nebulizer uptake during study follow-up

Of the 1,866 participants who indicated no nebulizer use at baseline, 237 subsequently reported uptake at a later visit. In the ICPH model, nebulizer uptake was significantly associated with: a history of asthma (HR 1.87, 95%CI[1.42,2.47]); at least one COPD exacerbation in the year prior to any post-baseline study visit (HR 1.87, 95%CI[1.37,2.55]); CAT Score ≥10 (HR 3.05, 95%CI[1.94,4.82]); and per liter decrease in FEV_1 (HR 2.07, 95%CI [1.62,2.64]) (Table 3). These findings were robust to independent sensitivity analyses in TEPS and COPD participants (Supplemental Table 3).

The overall median time to nebulizer uptake was 102 months among those not using nebulizers at study entry (Figure 2). The Kaplan-Meier cumulative incidence function (Figure 2)

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shows a significantly earlier initiation of nebulizers among those with more exacerbations,CAT Score ≥ 10, and among COPD vs TEPS (log-rank P < 0.001 for all). For those not using nebulizers at V1, the median time to nebulizer uptake varied by exacerbations (93, 85, or 74 months for one, two, or three or more exacerbations, respectively). Among those without exacerbations in the year prior to V1, 37% had started using nebulizers by V5. Among those not using nebulizers at V1 with CAT score <10, 26% had started using nebulizers by V5, whereas among those with CAT ≥10 at V1the median time to nebulizer uptake was 96 months. Among TEPS not using nebulizers at V1, 31% had started using nebulizers by V5, and among participants with COPD not using nebulizers at V1 the median time to nebulizer use was 97 months.

Description of Nebulized Medication Type

Of the 17.5%(194/1,136) participants who reported nebulizer use at V5, 73%(142/194) indicated only as-needed use (Supplemental Table 4). Eighty-seven percent(170/194) used short-acting bronchodilators, and 3%(6/194) used long-acting bronchodilators or corticosteroids. Use of long-acting bronchodilators or other nebulized treatments, including hypertonic saline and "other" not defined, accounted for 7%(14/194). Additionally, among baseline nebulizer users, 92% used bronchodilators and 71% used inhaled steroids in the prior three months. (Supplemental Table 4).

Discussion

This post-hoc analysis of a multicenter, prospective, observational cohort study reports the prevalence and patterns of nebulized drug utilization in individuals with smoking histories with or without spirometrically defined COPD. This study adds to the existing literature by evaluating nebulizer uptake over time in both COPD and TEPS populations. In contrast to prior large studies

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of nebulizer use, which have primarily been cross-sectional, our longitudinal design allowed for assessment of changes in utilization patterns and provides insight into real-world prescribing beyond single time-point estimates. Our data reveal that the factors most strongly associated with nebulizer use at baseline were increased frequency of respiratory exacerbations, decreased exercise capacity, low lung function, and greater respiratory symptom burden among TEPS and patients with COPD. In longitudinal analysis, moderate to severe respiratory exacerbations in the year before each visit had the largest effect size on new nebulizer use, and those with more frequent exacerbations showed earlier uptake. Similar to the cross-sectional analysis, greater symptom burden was associated with uptake, however decreased exercise capacity did not remain an independent predictor in the longidutinal analysis. Overall, these results support prior studies and should motivate specific investigation into the efficacy of nebulizer use in the management of both COPD and TEPS.

Among participants with advanced COPD, defined as either GOLD spirometric Stage 4 or GOLD Group D, nearly half used nebulizers. Although current professional society guidelines do not preferentially recommend nebulizers to manage chronic COPD symptoms, efficacy is generally considered similar to handheld devices.[13,36,37] This assumption is influenced by similar short-term improvement in lung function in comparisons of hand-held inhalers versus nebulizers in patients who demonstrated proper technique of inhaler use.[19]

Whether significant clinical benefits were derived in our cohort from nebulizer use is outside the scope of this analysis. Nevertheless, according to previous studies, COPD patients with severe disease burden may perceive greater symptom relief from nebulized medications, due to their ease of use relative to hand-held inhalers (i.e., minimal need for breath coordination or optimal inspiratory effort).[5,38–41] Asthma patients similarly show increased nebulizer use with

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severe symptoms.[42] Additionally, clinicians may hold similar beliefs and experience difficulty teaching proper inhaler technique, especially in those with advanced COPD, older age, and impaired cognition.[38] Both patient and clinician factors likely influence nebulizer utilization. Furthermore, our study highlights the association between nebulizer use and exacerbations, which often lead to emergency room visits and hospitalizations where patients may receive nebulized therapies in the hospital and upon discharge.[43,44]

Additionally, we made the novel finding that a substantial number of TEPS reported nebulizer use, a finding associated with respiratory exacerbations in the longitudinal analysis. TEPS represent a distinct subset, analogous to COPD Stage 0 or "pre-COPD," and are at an elevated risk of disease progression.[45] An investigation conducted by McKleroy *et al*. in the SPIROMICS cohort found that while rates of FEV_1 decline or incidence of COPD were not increased when comparing symptomatic to asymptomatic TEPS, symptomatic TEPS had significantly more exacerbations.[17] Nevertheless, the use of maintenance inhaled bronchodilators may not significantly improve symptom control in TEPS.[46] However, we showed that nebulizer uptake among TEPS was associated with greater respiratory symptom burden. Our findings are noteworthy in showing that real-world nebulizer utilization is not always associated with advanced COPD or age; but that it does represent a relevant drug delivery option even among those with early disease; as technology continues to evolve, patterns of usage may also change.[47]

Participants with COPD and TEPS predominantly used nebulizers to deliver short-acting bronchodilators. This suggests use during acute dyspnea events, akin to nebulizer utilization for acute exacerbations in hospital settings.[3] By contrast, few used nebulized long-acting bronchodilators or corticosteroids.. This finding is unsurprising, as the landscape of nebulized medications is evolving rapidly, with only recent approval of nebulized LAMAs, (glycopyrrolate

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and revefenacin), and the phosphodiesterase-3/-4 inhibitor ensifentrine.[3,48] These marked a significant milestone in novel treatment options for advanced COPD. Future studies should evaluate the benefits of nebulized long-acting therapies to optimize outcomes in COPD.

Another novel finding is that nebulizer users were on average younger than non-users (62 vs. 64 years), although after adjusting for other factors in cross-sectional multivariable analysis, age was not a significant predictor. This finding contrasts with studies showing more frequent nebulizer use among older COPD patients.[49] Other previously demonstrated associations were with lower FEV_1% and with greater air trapping, which causes lower IC, but these have not been rigorously analyzed in multivariable models.[49] Reduced IC is linked to poor peak inspiratory flow rates, a known factor limiting efficacy of MDIs and DPIs.[49] Given this, we can hypothesize that reduced IC may drive nebulizer use. However more investigation into the patterns and efficacy of nebulizer use would clarify this relationship. In agreement, nebulizers users in our study on average had a statistically significantly lower IC, and in bivariate analysis, lower IC was predictive of nebulizer use.[49] However, we were unable to evaluate IC in the multivariable model due to collinearity. Future studies using plethysmography to measure subdivisions of lung volume are needed to explore the roles of air trapping and hyperinflation.

Socioeconomic and racial disparities were apparent in the baseline unadjusted analyses but attenuated in multivariable models, suggesting that clinical disease characteristics may underlie the observed demographic variation. The association between socioeconomic disadvantage and nebulizer use is consistent with prior findings linking lower socioeconomic status and education attainment to worse COPD symptom control and outcomes, as well as poorer inhaler technique and adherence.[21,26,50,51] We found more frequent nebulizer use among Black participants, those with lower incomes and greater neighborhood disadvantage. One potential explanation is the

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relatively low cost of nebulized short-acting bronchodilators relative to MDIs (approximately 10 times greater cost per dose for albuterol-ipratropium).[22] Future investigation should assess the effect of health insurance on nebulizer use, which was out of the scope of this analysis. Additionally, higher odds of nebulizer use among women suggest sex-specific differences in disease presentation or healthcare utilization that merit further investigation.

Limitations and Strengths

Our study has several limitations. First, as an observational non-randomized study, we cannot assumecausality of the demonstrated associations. Second, we recruited participants from large academic medical centers, which may impact generalizability. Third, the frequency of nebulizer use and the distinction between maintenance vs. rescue medications were collected only at V5. Although V5 was included in the time-to-event analysis to preserve longitudinal follow-up, the altered exposure definition at this visit may introduce misclassification and should be considered when interpreting hazard estimates. Fourth, nebulizer use was self-reported, potentially introducing recall bias. Fifth, the time-to-event analysis ignored participants whose nebulizer use varied from between visits, as we censored subjects at the first visit reporting nebulizer use; this approach misses granularity in subsequently variable nebulizer usage. Sixth, because few participants used long-acting nebulized medications, our results primarily represent users of short-acting nebulized medications and should be interpreted in this context. Seventh, because the milieu of both long-acting hand-held and nebulized therapies and the GOLD treatment guidelines evolved substantially over the course of the study period, we did not control for concurrent handheld inhaled medication use in our analyses, as they would have complicated our models substantially. However, strengths of our design include its longitudinal, prospective nature, which, by taking into

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account time-variant characteristics of disease progression, identified temporal patterns in nebulizer uptake. Additionally, our use of an interval-censored modeling approach accounts for uncertainty in the exact time between study visits at which nebulizer use began. This approach provides highly reliable estimates for hypothesis generation to design future trials.

Conclusion

Nebulized medication delivery systems are widely used among SPIROMICS participants with smoking histories, regardless of the presence of spirometrically defined COPD. Nearly half of individuals in GOLD Group D reported nebulizer use at study enrollment, and many participants in all GOLD groups initiated nebulizer use over the study period, yet long-acting maintenance therapies were infrequently utilized. Nebulizer use was associated with previous respiratory exacerbations, symptoms, and diminished exercise capacity. Although our observational study design precludes assessment of causality, these findings argue for randomized controlled trials to compare directly the efficacy of nebulized versus hand-held devices, particularly in patients with advanced COPD with high symptom burden and frequent exacerbations.

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Author Contributions:
All authors contributed to enrolling participants, conducting study procedures, and generating data for analysis.
JCF, DM, RGBuhr, and IB conceived the design of the analysis.
JCF conducted the analyses with guidance from DM and RGBuhr and attests to their validity.
JCF, AH, RGBuhr, DPT, IB drafted the manuscript with critical editing from all co-authors.
All coauthors reviewed the final manuscript and approved it for publication.

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Author disclosure forms have been provided with the submission.

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Drs. Buhr, Curtis, Fortis, and Paine are employees of the Veterans Health Administration. The findings and positions in this manuscript do not necessarily reflect those of the Department of Veterans Affairs or the United States Government.

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REFERENCES

1. Bonini M. The importance of inhaler devices in the treatment of COPD. Published online 2015:9.
2. Roman-Rodriguez M, Kaplan A. GOLD 2021 Strategy Report: Implications for Asthma–COPD Overlap. *Int J Chron Obstruct Pulmon Dis*. 2021;16:1709-1715. doi:10.2147/COPD.S300902
3. Barjaktarevic IZ, Milstone AP. Nebulized Therapies in COPD: Past, Present, and the Future. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1665-1677. doi:10.2147/COPD.S252435
4. Ding B, Small M, Scheffel G, Holmgren U. Maintenance inhaler preference, attribute importance, and satisfaction in prescribing physicians and patients with asthma, COPD, or asthma–COPD overlap syndrome consulting for routine care. *Int J Chron Obstruct Pulmon Dis*. 2018;13:927-936. doi:10.2147/COPD.S154525
5. Hanania NA, Braman S, Adams SG, et al. The Role of Inhalation Delivery Devices in COPD: Perspectives of Patients and Health Care Providers. *Chronic Obstr Pulm Dis J COPD Found*. 2018;5(2):111-123. doi:10.15326/jcopdf.5.2.2017.0168
6. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respir Res*. 2018;19:10. doi:10.1186/s12931-017-0710-y
7. *Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of COPD 2017 [Cited 2024 July 16]. Available from: Http://Goldcopd.Org/.*
8. Usmani OS, Hickey AJ, Guranlioglu D, et al. The Impact of Inhaler Device Regimen in Patients with Asthma or COPD. *J Allergy Clin Immunol Pract*. 2021;9(8):3033-3040.e1. doi:10.1016/j.jaip.2021.04.024
9. Vanoverschelde A, van der Wel P, Putman B, Lahousse L. Determinants of poor inhaler technique and poor therapy adherence in obstructive lung diseases: a cross-sectional study in community pharmacies. *BMJ Open Respir Res*. 2021;8(1):e000823. doi:10.1136/bmjresp-2020-000823
10. Rootmensen GN, van Keimpema ARJ, Jansen HM, de Haan RJ. Predictors of Incorrect Inhalation Technique in Patients with Asthma or COPD: A Study Using a Validated Videotaped Scoring Method. *J Aerosol Med Pulm Drug Deliv*. 2010;23(5):323-328. doi:10.1089/jamp.2009.0785
11. Sanchis J, Gich I, Pedersen S, Aerosol Drug Management Improvement Team (ADMIT). Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? *Chest*. 2016;150(2):394-406. doi:10.1016/j.chest.2016.03.041
12. Hua J lan, Ye X fen, Du C ling, et al. Optimizing inhalation therapy in the aspect of peak inhalation flow rate in patients with chronic obstructive pulmonary disease or asthma. *BMC Pulm Med*. 2021;21:302. doi:10.1186/s12890-021-01674-5
13. Terry PD, Dhand R. Maintenance Therapy with Nebulizers in Patients with Stable COPD: Need for Reevaluation. *Pulm Ther*. 2020;6(2):177-192. doi:10.1007/s41030-020-00120-x
14. Sharafkhaneh A, Wolf RA, Goodnight S, Hanania NA, Make BJ, Tashkin DP. Perceptions and Attitudes Toward the Use of Nebulized Therapy for COPD: Patient and Caregiver Perspectives. *COPD J Chronic Obstr Pulm Dis*. 2013;10(4):482-492. doi:10.3109/15412555.2013.773302

Published online February 25, 2026 https://doi.org/10.15326/jcopdf.2025.0714

15. Dhand R, Hess MW, Yohannes AM. Recalibrating Perceptions and Attitudes Toward Nebulizers versus Inhalers for Maintenance Therapy in COPD: Past as Prologue. *Int J Chron Obstruct Pulmon Dis*. 2024;19:2571-2586. doi:10.2147/COPD.S491275
16. Woodruff PG, Barr RG, Bleecker E, et al. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med*. 2016;374(19):1811-1821. doi:10.1056/NEJMoa1505971
17. McKleroy W, Shing T, Anderson WH, et al. Longitudinal Follow-Up of Participants With Tobacco Exposure and Preserved Spirometry. *JAMA*. 2023;330(5):442-453. doi:10.1001/jama.2023.11676
18. Han MK, Ye W, Wang D, et al. Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function. *N Engl J Med*. 2022;387(13):1173-1184. doi:10.1056/NEJMoa2204752
19. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest*. 2005;127(1):335-371. doi:10.1378/chest.127.1.335
20. Terry PD, Dhand R. The 2023 GOLD Report: Updated Guidelines for Inhaled Pharmacological Therapy in Patients with Stable COPD. *Pulm Ther*. 2023;9(3):345-357. doi:10.1007/s41030-023-00233-z
21. Duarte-de-Araújo A, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: misuse of inhaler devices in clinical practice. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1209-1217. doi:10.2147/COPD.S178040
22. Gregory KL, Wilken L, Hart MK. *Pulmonary Disease Aerosol Delivery Devices: A Guide for Physicians, Nurses, Pharmacists, and Other Health Care Professionals*. American Association for Respiratory Care; 2017. https://www.aarc.org/wp-content/uploads/2018/01/aerosol-guide-for-hcp-3rd.pdf
23. Couper D, LaVange LM, Han M, et al. DESIGN OF THE SUBPOPULATIONS AND INTERMEDIATE OUTCOMES IN COPD STUDY (SPIROMICS). *Thorax*. 2014;69(5):492-495. doi:10.1136/thoraxjnl-2013-203897
24. Area Deprivation Index. University of Wisconsin School of Medicine and Publice Health. 2020. https://www.neighborhoodatlas.medicine.wisc.edu
25. Kind AJH, Buckingham WR. Making Neighborhood-Disadvantage Metrics Accessible — The Neighborhood Atlas. *N Engl J Med*. 2018;378(26):2456-2458. doi:10.1056/NEJMp1802313
26. Galiatsatos P, Woo H, Paulin LM, et al. The Association Between Neighborhood Socioeconomic Disadvantage and Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis*. 2020;15:981-993. doi:10.2147/COPD.S238933
27. Kim V, Zhao H, Regan E, et al. The St. George's Respiratory Questionnaire Definition of Chronic Bronchitis May Be a Better Predictor of COPD Exacerbations Compared With the Classic Definition. *Chest*. 2019;156(4):685-695. doi:10.1016/j.chest.2019.03.041
28. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159(1):179-187.
29. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117. doi:10.1164/ajrccm.166.1.at1102

Published online February 25, 2026 https://doi.org/10.15326/jcopdf.2025.0714

30. Myers J, Bader D, Madhavan R, Froelicher V. Validation of a specific activity questionnaire to estimate exercise tolerance in patients referred for exercise testing. *Am Heart J*. 2001;142(6):1041-1046. doi:10.1067/mhj.2001.118740
31. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648-654. doi:10.1183/09031936.00102509
32. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(7):581-586. doi:10.1136/thx.54.7.581
33. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992;145(6):1321-1327. doi:10.1164/ajrccm/145.6.1321
34. Goggins WB, Finkelstein DM. A proportional hazards model for multivariate interval-censored failure time data. *Biometrics*. 2000;56(3):940-943. doi:10.1111/j.0006-341x.2000.00940.x
35. Finkelstein DM. A Proportional Hazards Model for Interval-Censored Failure Time Data. *Biometrics*. 1986;42(4):845-854. doi:10.2307/2530698
36. Co-Chairmen of the Task Force:, Boe J, Dennis JH, et al. European Respiratory Society Guidelines on the use of nebulizers: Guidelines prepared by a European Respiratory Society Task Force on the use of nebulizers. *Eur Respir J*. 2001;18(1):228-242. doi:10.1183/09031936.01.00220001
37. 2020 Gold Reports. Global Initiative for Chronic Obstructive Lung Disease - GOLD. Accessed June 6, 2022. https://goldcopd.org/gold-reports/
38. Melani AS, Canessa P, Coloretti I, et al. Inhaler mishandling is very common in patients with chronic airflow obstruction and long-term home nebuliser use. *Respir Med*. 2012;106(5):668-676. doi:10.1016/j.rmed.2011.11.016
39. Dhand R, Mahler DA, Carlin BW, et al. Results of a Patient Survey Regarding COPD Knowledge, Treatment Experiences, and Practices With Inhalation Devices. *Respir Care*. 2018;63(7):833-839. doi:10.4187/respcare.05715
40. Braman SS, Carlin BW, Hanania NA, et al. Results of a Pulmonologist Survey Regarding Knowledge and Practices With Inhalation Devices for COPD. *Respir Care*. 2018;63(7):840-848. doi:10.4187/respcare.05717
41. Melamed K, Cambridge L, Christiani D c., et al. Understanding Nebulizer Utilization in Clinical Practice: A COPD Foundation Nebulizer Consortium Survey Study. *Am J Respir Crit Care Med*. 2025;211(Abstracts):A7140-A7140. doi:10.1164/ajrccm.2025.211.Abstracts.A7140
42. Krishnan JA, Demott M, McCoy JV, Chanmugam A, Rand CS. Nebulized beta2-agonist use in high-risk inner-city adults with asthma. *J Asthma Off J Assoc Care Asthma*. 2003;40(4):367-373. doi:10.1081/jas-120018636
43. Foster AA, Stoll J, Daly CJ, Clark CM, Sethi S, Jacobs DM. Patient and social factors related to nebulizer use in COPD patients at the transition of care: a qualitative study. *BMC Pulm Med*. 2023;23:358. doi:10.1186/s12890-023-02651-w
44. Kopsaftis ZA, Sulaiman NS, Mountain OD, Carson-Chahhoud KV, Phillips PA, Smith BJ. Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: systematic review. *Syst Rev*. 2018;7(1):213. doi:10.1186/s13643-018-0860-0

Published online February 25, 2026 https://doi.org/10.15326/jcopdf.2025.0714

45. Han MK, Agusti A, Celli BR, et al. From GOLD 0 to Pre-COPD. *Am J Respir Crit Care Med*. 2021;203(4):414-423. doi:10.1164/rccm.202008-3328PP
46. Han MK, Ye W, Wang D, et al. Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function. *N Engl J Med*. 2022;387(13):1173-1184. doi:10.1056/NEJMoa2204752
47. Troy M, Van Vleet J, Tashkin D, Barjaktarevic I. Recent advances predict a bright future for nebulizers. *Curr Opin Pulm Med*. 2023;29(2):123-132. doi:10.1097/MCP.0000000000000941
48. Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease: Randomized, Double-Blind, Placebo-controlled, Multicenter Phase III Trials (the ENHANCE Trials). doi:10.1164/rccm.202306-0944OC
49. Loh CH, Peters SP, Lovings TM, Ohar JA. Suboptimal Inspiratory Flow Rates Are Associated with Chronic Obstructive Pulmonary Disease and All-Cause Readmissions. *Ann Am Thorac Soc*. 2017;14(8):1305-1311. doi:10.1513/AnnalsATS.201611-903OC
50. Gershon AS, Dolmage TE, Stephenson A, Jackson B. Chronic Obstructive Pulmonary Disease and SocioEconomic Status: a Systematic Review. *COPD J Chronic Obstr Pulm Dis*. 2012;9(3):216-226. doi:10.3109/15412555.2011.648030
51. Turan O, Turan PA, Mirici A. Parameters affecting inhalation therapy adherence in elderly patients with chronic obstructive lung disease and asthma. *Geriatr Gerontol Int*. 2017;17(6):999-1005. doi:10.1111/ggi.12823

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Tables and Figures:

Table 1. Baseline demographics and medical history by nebulizer use group

	No Baseline Nebulizer use N =1,882	**Baseline Nebulizer use** N=265	**P-value**
Age (years), mean (SD)	64.0 (8.8)	62.0 (8.4)	<0.001
Male	55%	47%	0.009
BMI (kg/m^2), mean (SD)	27.9 (5.1)	27.5 (5.9)	0.250
Race			
White	79%	69%	<0.001
Black	17%	27%	
Other	4%	4%	
Hispanic/Latino Ethnicity	4%	3%	0.510
ADI national rank percentile, mean (SD)	36.8 (27.7)	45.2 (28.7)	<0.001
Yearly household income			
<$15,000	18%	31%	<0.001
$15,000-$34,999	19%	20%	
$35,000-$49,999	13%	10%	
$50,000-$74,999	15%	13%	
$75,000 or more	19%	10%	
Declined to answer	16%	17%	
Diagnosis of COPD at study entry	64%	87%	<0.001
Current Tobacco Smoking	39%	34%	0.099
Ever diagnosed with asthma	18%	43%	<0.001
Chronic Bronchitis by SGRQ	42%	60%	<0.001
GOLD Stage of COPD Severity			
0	36%	13%	<0.001
1	16%	5%	
2	31%	29%	
3	13%	35%	
4	4%	18%	
GOLD Grade*			
A	43%	22%	<0.001
B	11%	24%	
C	4%	17%	
D	3%	21%	
FEV_1 (*% Predicted*), mean (SD)	77 (25)	52 (24)	<0.001
FEV_1 (*L*), mean (SD)	2.2 (0.9)	1.4 (0.7)	<0.001
Inspiratory Capacity (*L*), mean (SD)	2.7 (0.8)	2.2 (0.8)	<0.001
Exacerbations in year prior to enrollment			
None	83%	56%	<0.001
One	11%	23%	
Two	4%	10%	
Three or more	3%	11%	
CAT Score, mean (SD)	12.8 (7.8)	20.5 (7.7)	<0.001
SGRQ Score, mean (SD)*	30.0 (19.3)	52.0 (16.0)	<0.001
mMRC Score*			
0	34%	8%	<0.001
1	45%	38%	
2	13%	29%	
3	6%	18%	
4	1%	6%	
VSAQ Score, mean (SD)	5.7 (2.8)	3.4 (1.9)	<0.001
6 minute walk distance (*m*), mean (SD)	410 (107)	323 (113)	<0.001

*Variables with different denominators, SGRQ n=1,745 (n=147 missing), VSAQ n= 1,812 (n=74 missing), mMRC 2,138 (n=9 missing), GOLD Grade

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n=1392 (n=755 missing)

Table 2: Odds Ratios from Bivariate and Multivariable Logistic Regression Predicting Nebulizer use at Baseline.

	Bivariate Analysis				Multivariable Analysis			
	Odds Ratio	95% Confidence Interval		P Value	Odds Ratio	95% Confidence Interval		P Value
Age (per year increase)	0.974	0.961	0.988	<0.001	0.949	0.929		<.001
Male (ref. female)	0.710	0.549	0.919	<0.001	1.430	1.034	1.978	0.031
Race (ref. white)								
Black	1.790	1.329	2.419	<0.001	1.308	0.893	1.915	0.169*
Other	1.071	1.33	2.419	0.835	1.074	0.511	2.257	0.852
BMI (per unit increase)	0.985	0.961	1.01	0.248	0.991	0.963	1.019	0.511
ADI (ref. 0 to 25th percentile)								
26 to 50th percentile	1.093	0.776	1.538	0.611	0.871	0.589	1.287	0.487
51st to 75th percentile	1.476	1.049	2.075	0.025	0.799	0.532	1.201	0.280*
76th to 100th percentile	1.966	1.338	2.889	0.001	0.875	0.548	1.394	0.573*
Income (ref. <$15,000))								
$15,000-$34,999	0.623	0.428	0.908	0.623	0.726	0.466	1.131	0.157
$35,000-$49,999	0.439	0.274	0.703	0.001	0.563	0.327	0.972	0.039
$50,000-$74,999	0.486	0.316	0.747	<0.001	0.777	0.461	1.310	0.344
$75,000 or more	0.294	0.184	0.468	<0.001	0.615	0.348	1.090	0.096
Declined to answer	0.597	0.401	0.890	<0.001	0.692	0.432	1.107	0.124
COPD (ref. TEPS)	3.734	2.585	5.395	<0.001	1.088	0.658	1.797	0.743*
Current Smoking (ref. not smoking)	0.790	0.602	1.036	0.088	0.603	0.416	0.874	0.008*
Ever diagnosed with asthma	3.512	2.780	4.603	<0.001	2.408	1.756	3.301	0.000
Chronic Bronchitis by SGRQ	2.032	1.564	2.641	<0.001	1.509	1.102	2.066	0.010
FEV_1 (per liter decrease)	3.704	3.021	4.545	<0.001	2.805	2.090	3.767	0.000
Inspiratory Capacity (per liter increase)	0.482	0.401	0.579	<0.001	‡			
SGRQ	1.057	1.049	1.065	<0.001	‡			
VSAQ	0.647	0.602	0.695	<0.001	‡			
Exacerbations (ref. none)								
One	3.247	3.327	4.530	<0.001	1.815	1.245	2.644	0.002
Two	4.124	2.563	6.638	<0.001	1.861	1.075	3.223	0.027
Three or more	5.558	3.238	8.985	<0.001	1.875	1.072	3.279	<0.001
CAT Score ≥10 (ref <10)	6.193	4.060	9.445	<0.001	1.886	1.173	3.033	<0.001
6MWD (per 10 meter decrease)	1.071	1.058	1.083	<0.001	1.030	1.016	1.045	<.001

*Indicates change of significance in adjusted model compared to bivariate analysis

‡ Indicates that variable was not included in multivariable model due to collinearity.

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Table 3: Hazard ratios of interval censored proportional hazards model predicting nebulizer uptake during the study period.

	Hazard Ratio	[95% Confidence Interval]		P-Value
Age at Visit 1	0.970	0.952	0.989	0.002
Race (ref. white)				
Black	1.084	0.774	1.517	0.640
Other	0.696	0.310	1.563	0.380
BMI (per unit change)	1.019	0.993	1.045	0.148
ADI (ref. 0 to 25th percentile)				
26 to 50th percentile	0.968	0.677	1.383	0.858
51st to 75th percentile	1.250	0.861	1.814	0.240
76th to 100th percentile	1.127	0.758	1.676	0.555
Household Income (ref. <$15,000)				
$15,000-$34,999	1.110	0.751	1.641	0.601
$35,000-$49,999	1.043	0.656	1.658	0.860
$50,000-$74,999	1.017	0.617	1.678	0.947
$75,000 or more	0.695	0.392	1.235	0.215
Declined to answer	1.318	0.867	2.006	0.197
COPD (ref TEPS)	1.458	0.965	2.202	0.073
Current Smoking (ref. not smoking)	1.109	0.796	1.545	0.540
Ever diagnosed with asthma	1.868	1.415	2.466	<0.001
Chronic Bronchitis by SGRQ	0.778	0.588	1.029	0.079
Exacerbations (ref. None)				
One	1.866	1.365	2.552	<0.001
Two	1.155	0.727	1.836	0.542
Three or more	0.873	0.502	1.516	0.628
CAT Score ≥10 (ref. <10)	3.053	1.935	4.815	<0.001
FEV_1 (per liter decrease)	2.072	1.622	2.646	<0.001
6MWD (per 10 meter decrease)	1.009	0.996	1.023	0.161

Model adjusted for baseline (non-time varying) race; Age at Visit 1; ADI, area deprivation index quartile; income; history of COPD; current smoking status. Time varying covariates included: BMI, Body Mass Index; exacerbations in the last year; CAT Score, COPD assessment test score; FEV1, forced expiratory volume in 1 second; and 6MWD, six minute walk distance.

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Figure titles and legends

Figure 1

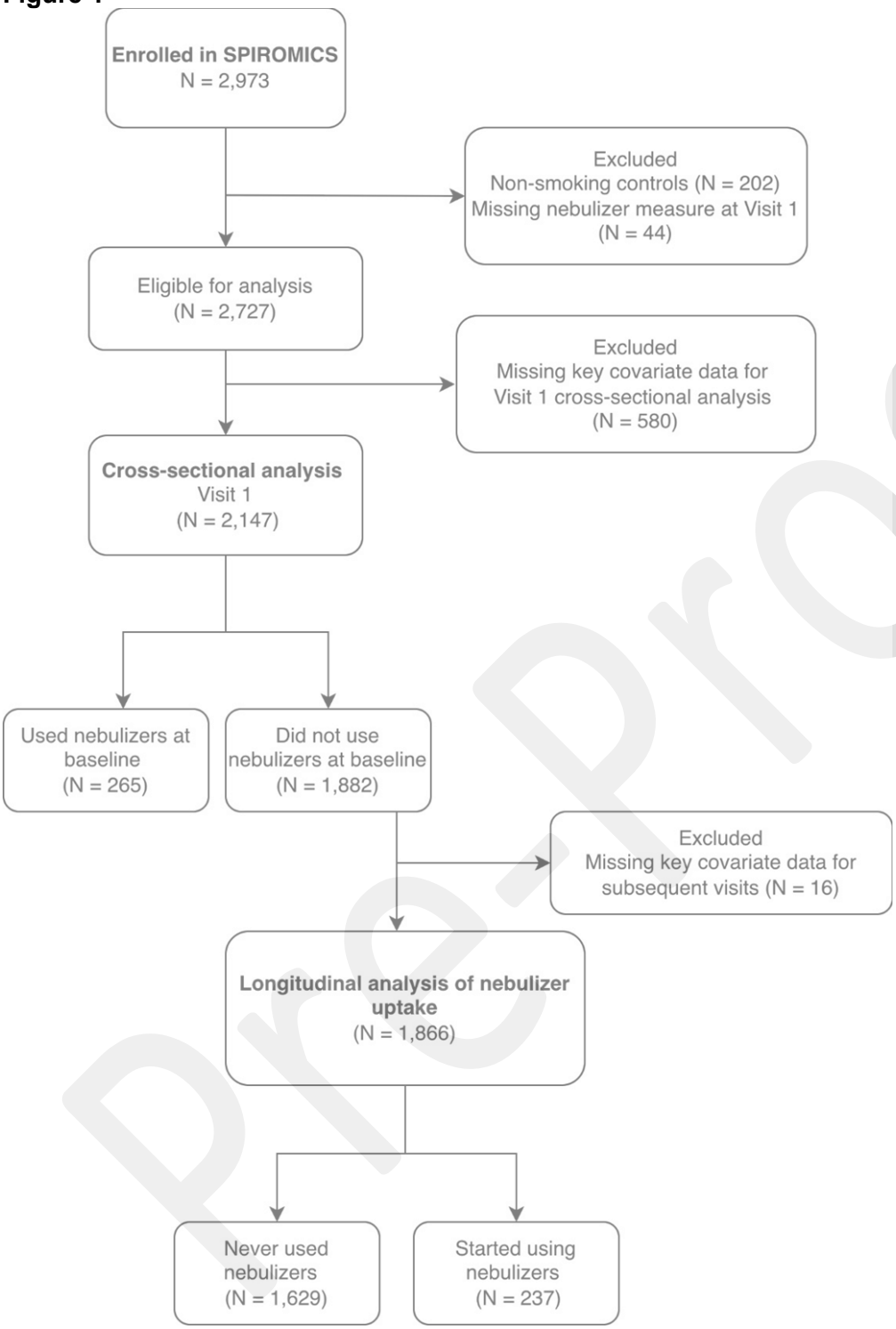

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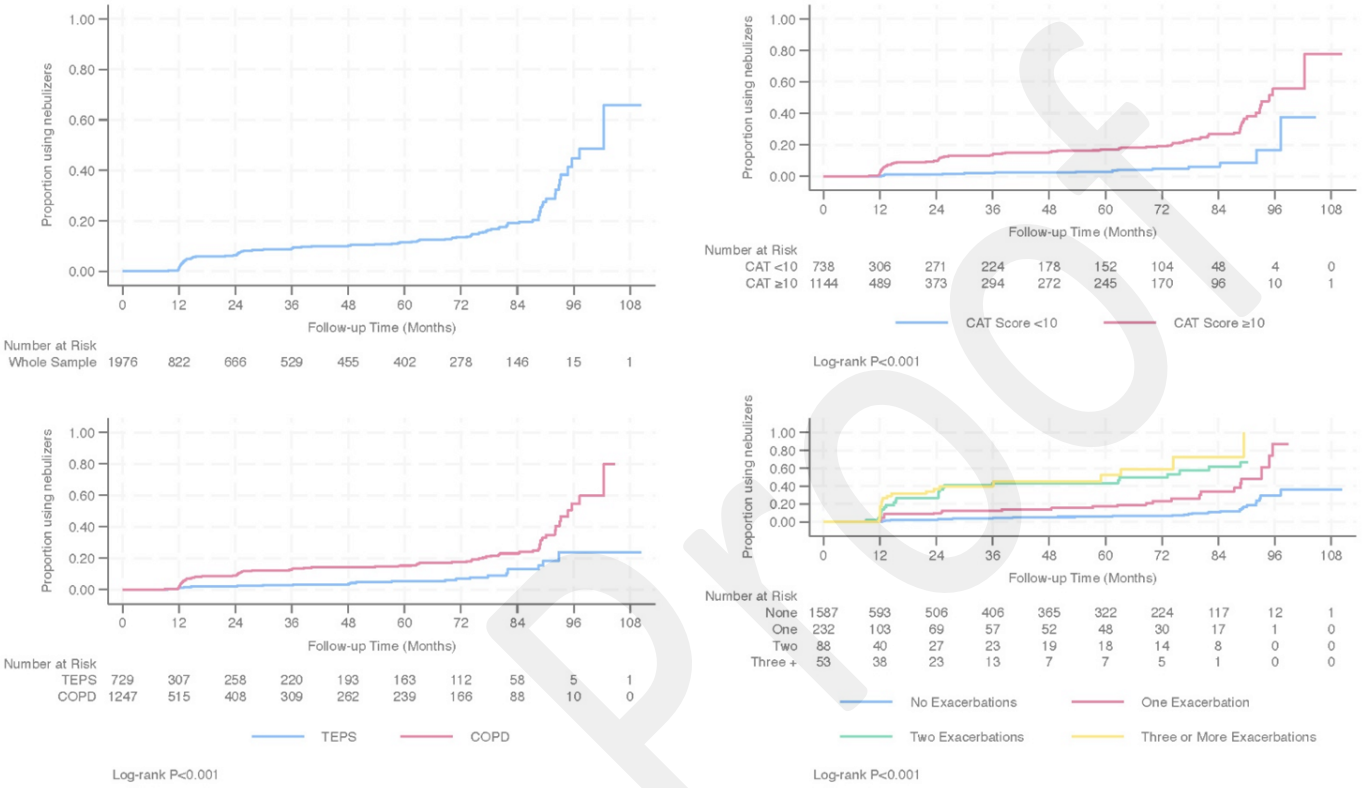
Figure 2



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Supplemental Materials

Visits 1 - 4

Have you used nebulized bronchodilators in the past 3 months?

1) Yes
2) No →Skip next question
3) Don't know →Skip next question

Which nebulized bronchodilators have you used in the past 3 months? Yes/No (check all that apply)

1) formoterol (Perforomist).
2) arformoterol (Brovana)
3) albuterol and ipratropium bromide (DuoNeb)
4) albuterol (Proventil, Ventolin, ProAir)
5) ipratropium bromide (Atrovent)

Visit 5

Are you regularly using any nebulized medications

1) No →Skip next question
2) Yes

How often (daily versus as needed when having difficulties)?

1) Daily
2) As needed when having difficulties

Which medications? (Check all that apply)

1) Accuneb (albuterol sulfate) nebulizer
2) Xopenex (levalbuterol) nebulizer
3) Atrovent (ipratropium) nebulizer
4) DuoNeb (ipratropium bromide/albuterol) nebulizer
5) Performist (formoterol) nebulizer
6) Brovana (arfomoterol) nebulizer
7) Pulmicort (budesonide) nebulizer
8) 3% Hypertonic saline
9) 7% Hypertonic saline
10) Other, please specify _____

Supplemental Figure 1. *Participant Survey on Nebulized Medication Use.* This figure presents questions used to assess participants' use of nebulized bronchodilators and other medications. Initial questions (Visits 1-4) identify recent use of specific bronchodilators, while questions at Visit 5 assess regular usage patterns, frequency, and specific types of nebulized medications.

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Supplemental Table 1. Baseline demographics and clinical characteristics by TEPS versus COPD and Nebulizer Use Group

	TEPS		COPD	
	No Nebulizer Use (N = 682)	**Nebulizer Use** (N = 35)	**No Nebulizer Use** (N = 1,200)	**Nebulizer Use** (N = 230)
Age (years), mean (SD)	60.9 (9.5)	58.2 (8.3)	65.8 (7.9)	62.6 (8.3)
Male sex	48%	26%	60%	50%
Race				
White	70%	46%	84%	73%
Black	24%	49%	13%	23%
Other	6%	6%	4%	4%
Hispanic/Latino Ethnicity	6%	11%	3%	2%
ADI national rank percentile, mean (SD)	36.0 (27.6)	51.2 (29.0)	37.3 (27.8)	44.3 (28.6)
Yearly household income				
<$15,000	22%	46%	15%	28%
$15,000-$34,999	16%	20%	20%	20%
$35,000-$49,999	11%	11%	14%	10%
$50,000-$74,999	15%	6%	16%	14%
$75,000 or more	20%	9%	19%	10%
Declined to answer	16%	9%	16%	18%
BMI (kg/m^2), mean (SD)	29.0 (5.0)	31.5 (5.4)	27.3 (5.1)	26.9 (5.7)
Current Smoking (ref: not smoking)	48%	43%	34%	33%
Ever diagnosed with asthma	14%	60%	20%	40%
Chronic Bronchitis by SGRQ	37%	77%	45%	57%
FEV_1 (Percent Predicted), mean (SD)	97 (13)	89 (12)	65 (22)	47 (20)
FEV_1 (*L*), mean (SD)	2.8 (0.7)	2.4 (0.5)	1.9 (0.8)	1.3 (0.6)
Inspiratory Capacity (*L*), mean (SD)	2.8 (0.7)	2.5 (0.7)	2.6 (0.8)	2.2 (0.8)
Count of Exacerbations (year before enrollment)				
None	90%	69%	79%	54%
One	7%	14%	13%	24%
Two	2%	14%	5%	10%
Three or more	1%	3%	4%	12%
CAT Score, mean (SD)	10.8 (8.0)	21.7 (7.4)	13.9 (7.5)	20.4 (7.8)
SGRQ Score, mean (SD)	23.3 (18.6)	51.4 (16.2)	33.8 (18.6)	52.1 (16.0)
MMRC Score				
0	47%	11%	27%	8%
1	40%	43%	48%	37%
2	8%	31%	16%	29%
3	4%	9%	8%	19%
4	1%	6%	2%	6%
VSAQ Score, mean (SD)	6.5 (2.9)	3.1 (2.1)	5.3 (2.6)	3.4 (1.8)
6 Minute Walk Distance (*m*), mean (SD)	438 (91)	344 (106)	394 (112)	320 (114)

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Supplemental Table 2. Sensitivity Analysis of baseline logistic model for nebulizer use among COPD and TEPS groups.

	TEPS				COPD			
	Odds ratio	**Lower end of 95% CI**	**Upper end of 95% CI**	**P-Value**	**Odds ratio**	**Lower end of 95% CI**	**Upper end of 95% CI**	**P-Value**
Age (per year change)	0.948	0.888	1.013	0.115	0.948	0.927	0.969	<0.001
Male (ref. female)	1.230	0.372	4.063	0.734	1.458	1.036	2.052	0.031
Race (ref. White)								
Black	1.521	0.552	4.189	0.417	1.267	0.828	1.938	0.276
Other	0.844	0.146	4.895	0.850	1.035	0.450	2.381	0.935
BMI (per unit change)	0.989	0.906	1.079	0.805	0.992	0.962	1.022	0.587
ADI (ref. 0 to 25th percentile)								
26 to 50th percentile	0.858	0.271	2.720	0.795	0.832	0.544	1.271	0.394
51st to 75th percentile	0.922	0.284	2.992	0.893	0.788	0.507	1.225	0.290
76th to 100th percentile	1.409	0.411	4.832	0.586	0.808	0.482	1.356	0.420
Income (ref. <$15,000))								
$15,000-$34,999	0.623	0.200	1.942	0.415	0.766	0.469	1.249	0.285
$35,000-$49,999	0.653	0.149	2.857	0.572	0.557	0.306	1.013	0.055
$50,000-$74,999	0.286	0.043	1.894	0.194	0.891	0.509	1.561	0.688
$75,000 or more	0.720	0.138	3.767	0.697	0.606	0.326	1.124	0.112
Declined to answer	0.447	0.097	2.051	0.300	0.758	0.456	1.262	0.287
Current Smoking (ref. not smoking)	0.226	0.081	0.629	0.004	0.742	0.496	1.110	0.147
Ever diagnosed with asthma	4.399	1.838	10.531	0.001	2.067	1.462	2.923	<0.001
Chronic Bronchitis by SGRQ	2.710	1.052	6.977	0.039	1.314	0.935	1.846	0.116
FEV$_1$ (per liter decrease)	1.820	0.629	5.263	0.269	3.101	2.250	4.273	0.000
Exacerbations (ref. none)								
One	1.386	0.397	4.844	0.609	1.849	1.241	2.754	0.003
Two	9.586	2.300	39.952	0.002	1.488	0.822	2.695	0.189
Three or more	0.963	0.083	11.116	0.976	2.019	1.130	3.607	0.018
CAT Score (ref <10)	4.215	0.843	21.073	0.080	1.568	0.947	2.596	0.081
6MWD (per 10 m)	1.059	1.010	1.111	0.018	1.025	1.010	1.041	0.001

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Supplemental Table 3: Sensitivity analysis of Hazard ratios of interval censored proportional hazards model predicting nebulizer uptake during the study period for TEPS and COPD participants.

	TEPS				COPD			
	Hazard Ratio	**Lower limit of 95%CI**	**Upper limit of 95% CI**	**P-Value**	**Hazard ratio**	**Lower Limit of 95% CI**	**Upper Limit of 95% CI**	**P-Value**
Age at Visit 1 (years)	0.958	0.906	1.013	0.132	0.971	0.951	0.992	0.006
Race (ref. white)								
Black	0.857	0.341	2.157	0.744	1.162	0.794	1.702	0.439
Other	2.247	0.605	8.344	0.227	0.470	0.161	1.367	0.166
BMI (per unit change)	1.021	0.945	1.104	0.598	1.018	0.991	1.046	0.201
ADI (ref. 0 to 25th percentile)								
26 to 50th percentile	1.013	0.355	2.890	0.980	0.976	0.656	1.453	0.907
51st to 75th percentile	0.853	0.294	2.473	0.769	1.324	0.881	1.990	0.177
76th to 100th percentile	1.556	0.548	4.419	0.406	1.010	0.643	1.587	0.966
Income (ref. <$15,000))								
$15,000-$34,999	0.861	0.289	2.562	0.788	1.161	0.750	1.799	0.503
$35,000-$49,999	1.775	0.513	6.139	0.365	0.974	0.568	1.668	0.923
$50,000-$74,999	0.502	0.090	2.803	0.432	1.143	0.661	1.976	0.632
$75,000 or more	0.963	0.111	8.394	0.973	0.684	0.363	1.287	0.239
Declined to answer	2.069	0.852	5.023	0.108	1.256	0.771	2.046	0.361
Current Smoking (ref. not smoking)	1.417	0.463	4.336	0.542	1.069	0.746	1.532	0.716
Ever diagnosed with asthma	1.095	0.478	2.509	0.829	2.043	1.514	2.757	0.000
Chronic Bronchitis by SGRQ	1.042	0.478	2.270	0.917	0.746	0.546	1.019	0.065
Exacerbations (ref. None)								
One	4.234	1.643	10.912	0.003	1.671	1.182	2.362	0.004
Two	3.608	0.910	14.309	0.068	0.975	0.587	1.621	0.923
Three or more	1.289	0.232	7.166	0.772	0.809	0.442	1.482	0.493
CAT Score >10 (ref. <10)	1.951	0.586	6.501	0.276	3.552	2.033	6.207	0.000
FEV_1 (per liter decrease)	3.029	1.195	7.682	0.020	2.039	1.563	2.659	0.000
6MWD (per 10 meter decrease)	1.019	0.966	1.076	0.486	1.010	0.996	1.024	0.171

Model adjusted for baseline (non-time varying) race; Age at Visit 1; ADI, area deprivation index quartile; income; current smoking status. Time varying covariates included: BMI, Body Mass Index; exacerbations in the last year; CAT Score, COPD assessment test score; FEV_1, forced expiratory volume in 1 second; and 6MWD, six minute walk distance.

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Supplemental Table 4: Type of nebulized medication by daily versus as-needed use at Visit 5

	Overall (N=194)	Daily (N=52)	As Needed (N=142)	P-Value*
Short Acting Bronchodilators				
Albuterol	62% (120)	48% (25)	67% (95)	0.020
Levalbuterol	3% (6)	4% (2)	3% (4)	0.660
Ipratroprium Bromide	8% (16)	15% (8)	6% (8)	0.039
Albuterol-Ipratropium Bromide	19% (37)	29% (15)	16% (22)	0.041
Long Acting Bronchodilators				
Formoterol	<1% (1)	2% (1)	0% (0)	0.270
Arformoterol	<1% (1)	2% (1)	0% (0)	0.270
Budesonide	2% (4)	6% (3)	<1% (1)	0.060
3% sodium chloride	1% (2)	0% (0)	1% (2)	1.000
Other (Any not defined above)	6% (12)	2% (1)	8% (11)	0.190

*Fisher's exact test

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Supplemental Table 5: Hand-held inhaled medication by nebulizer use at Visit 1

	No Baseline Nebulizer Use (N=1,882)	Baseline Nebulizer Use (N=265)	Total (N=2,147)	p-value
Hand-held inhaled steroids used in the last three months at baseline				<0.001
No	1,307 (69%)	76 (29%)	1,383 (64%)	
Yes	571 (30%)	187 (71%)	758 (35%)	
Missing	4 (0%)	2 (1%)	6 (0%)	
Hand-held inhaled bronchodilators used in the last three months at baseline				<0.001
No	1,004 (53%)	21 (8%)	1,025 (48%)	
Yes	875 (46%)	243 (92%)	1,118 (52%)	
Missing	2 (0%)	1 (0%)	3 (0%)	

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