Treatment burden, clinical outcomes, and comorbidities in COPD: an examination of the utility of medication regimen complexity index in COPD

Netsanet A Negewo1,2
Peter G Gibson1,3
Peter AB Wark1,3
Jodie L Simpson1,2
Vanessa M McDonald1,4

1Priority Research Centre for Healthy Lungs, 2Hunter Medical Research Institute, Faculty of Health and Medicine, The University of Newcastle, Callaghan, 3Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, 4School of Nursing and Midwifery, Faculty of Health and Medicine, The University of Newcastle, Callaghan, NSW, Australia

Correspondence: Vanessa M McDonald
Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute Building, Level 2 West Wing, Locked Bag 1000, New Lambton, NSW 2305, Australia
Tel +61 2 4042 0146
Fax +61 2 4042 0046
Email vanessa.mcdonald@newcastle.edu.au

Objectives: The aim of this study was to explore the relationships of medication burden in COPD with clinical outcomes, comorbidities, and multidimensional indices.

Methods: In a cross-sectional study, COPD patients (n=222) were assessed for demographic information, comorbidities, medication use, and clinical outcomes. Complexity of medication regimens was quantified using the validated medication regimen complexity index (MRCI).

Results: Participants (58.6% males) had a mean (SD) age of 69.1 (8.3) years with a postbronchodilator forced expiratory volume in 1 second % predicted of 56.5 (20.4) and a median of five comorbidities. The median (q1, q3) total MRCI score was 24 (18.5, 31). COPD-specific medication regimens were more complex than those of non-COPD medications (median MRCI: 14.5 versus 9, respectively; P<0.0001). Complex dosage formulations contributed the most to higher MRCI scores of COPD-specific medications while dosing frequency primarily drove the complexity associated with non-COPD medications. Participants in Global Initiative for Chronic Obstructive Lung Disease quadrant D had the highest median MRCI score for COPD medications (15.5) compared to those in quadrants A (13.5; P=0.0001) and B (12.5; P<0.0001). Increased complexity of COPD-specific treatments showed significant but weak correlations with lower lung function and 6-minute walk distance, higher St George’s Respiratory Questionnaire and COPD assessment test scores, and higher number of prior year COPD exacerbations and hospitalizations. Comorbid cardiovascular, gastrointestinal, or metabolic diseases individually contributed to higher total MRCI scores and/or medication counts for all medications. Charlson Comorbidity Index and COPD-specific comorbidity test showed the highest degree of correlation with total MRCI score (ρ=0.289 and ρ=0.326; P<0.0001, respectively).

Conclusion: In COPD patients, complex medication regimens are associated with disease severity and specific class of comorbidities.

Keywords: medication burden, medication counts, complex pharmacotherapy, clinical scores

Introduction
COPD is a major public health problem and is expected to remain a challenge for health care systems well into the 21st century. Despite falling death rates, COPD is still among the leading causes of death worldwide. The disease burden associated with COPD is further exacerbated by the presence of comorbidities, which influence...
disease expression and survival. Pharmacotherapy is one of the principal approaches used in the management of COPD. Treatments for COPD can improve symptoms, health status, and exercise capacity, in addition to reducing the frequency and severity of exacerbations. People with COPD are also highly likely to be prescribed multiple other therapies, to effectively combat their nonrespiratory comorbid conditions. As a result, individuals with COPD may have complex medication regimens.

Complex pharmacotherapy is a key contributor to nonadherence, increased risk of drug–drug interactions and adverse drug events, poor disease control, and substantial cost of illness. As Winner pointed out, “the first step in minimizing complex medication regimens is to identify and quantify them.” The medication regimen complexity index (MRCI) is a tool that has been developed and validated for this purpose. MRCI measures the multiple aspects of medication regimens including type of dosage forms, dosing frequencies, and additional instructions that guide dosage administration. The relationships between MRCI and clinical outcomes including quality of life, unexplained hospitalization, all-cause mortality, readmission, and hospitalization for adverse drug events, and risk of hospital readmissions and/or emergency visits have been investigated. Although MRCI was originally developed and validated in people with COPD, so far only a few studies have applied this tool in studies involving COPD population. Nevertheless, these studies as such did not specifically investigate the relationships of MRCI with COPD-related clinical outcomes and other dimensions of the disease.

The present study aimed to explore the associations of medication burden in COPD patients, as measured by medication count and MRCI, with COPD outcomes (including disease severity, disease-specific health-related quality of life, exercise capacity, and prior year COPD exacerbation and hospitalization history) and multidimensional prognostic indices. Furthermore, we sought to determine the contributions of comorbid conditions to complex medication regimens in COPD. The two hypotheses we tested were that, 1) MRCI would be associated with COPD disease severity and comorbidities, and 2) MRCI may potentially serve as an alternative tool to the existing comorbidity-specific indices and other multidimensional COPD indices.

**Methods**

**Study design and participants**

This study was a cross-sectional study involving 222 COPD patients (postbronchodilator forced expiratory volume in 1 second [FEV₁] to forced vital capacity [FVC] ratio <0.70). The data for 72 participants were obtained from our previously published studies. The remaining 150 participants were recruited from the respiratory ambulatory care clinics at John Hunter Hospital (Newcastle, Australia), the clinical research databases of the Priority Research Centre for Healthy Lungs at the University of Newcastle and the Hunter Medical Research Institute (Newcastle, Australia), and through community advertisement. All participants provided written informed consent, and ethics approval was obtained from the Human Research Ethics Committee of the Hunter New England Local Health District (12/12/13.06) and the University of Newcastle (H-2013-0010).

**Clinical assessment**

Participants attended up to two visits and demographic information, lung function, smoking history, medical history, medication use, dyspnea (modified Medical Research Council [mMRC] scale), self-reported prior year exacerbation and hospitalization history, and health-related quality of life (St George’s Respiratory Questionnaire [SGRQ]) and COPD assessment test [CAT]) were recorded. Airflow limitation was assessed using spirometry (MedGraphics, CPFS/D USB™ Spirometer; BreezeSuite v7.1, Saint Paul, MN, USA) to measure pre- and postbronchodilator FEV₁, FVC, and FEV₁/FVC ratio. Severity of COPD was graded according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification system of airflow limitation based on postbronchodilator FEV₁ % predicted (ie, GOLD grade 1, FEV₁ ≥80%; GOLD grade 2, 50% ≤ FEV₁ <80%; GOLD grade 3, 30% ≤ FEV₁ <50%; GOLD grade 4, FEV₁ <30%). Participants were evaluated using GOLD quadrants according to the 2011 GOLD “ABCD” assessment tool (using mMRC for symptom assessment).

Participants also performed a 6-minute walk test.

**Comorbidities**

Comorbidities were recorded by interviewing participants using a medical history tool that examines 14 different body or organ systems. Participants were asked if they have any medical conditions relating to these organ systems. Self-reported comorbidity diagnosis was confirmed by reviewing patient’s medical records or current medications list.

**Exacerbation capture**

Exacerbation history was recorded by asking participants how many times in the last 12 months they experienced a COPD-related episode that led to hospitalization, emergency
visit, or the need for oral corticosteroids and/or antibiotic for at least 3 days.

Comorbidity-specific and other multidimensional COPD indices
Participants were evaluated using the following three comorbidity-specific indices, namely, Charlson Comorbidity Index (CCI),26 comorbidity test (COTE),27 and comorbidity, airway obstruction, dyspnea, and previous exacerbation (CODEX)28 and four multidimensional indices, namely, body mass index, airflow obstruction, dyspnea and exercise capacity (BODE),29 body mass index, airflow obstruction, dyspnea and severe exacerbations (BODEX),30 age, dyspnea and airflow obstruction (ADO),31 and dyspnea, airflow obstruction, smoking status and exacerbation (DOSE).32 All indices were calculated as previously prescribed.26–32

Medication assessment and MRCI scoring
Complexity of medication regimens was quantified using the MRCI developed and validated by George et al.3 MRCI is the summation of individual component scores for dosage form (section A), dosing frequency (section B), and medication administration instructions (section C). Higher MRCI scores indicate greater regimen complexity.3 Participants’ current prescription and nonprescription COPD and non-COPD medication lists were reviewed, and MRCI scores were calculated using the University of Colorado’s electronic MRCI Data Capture Tool13 and its accompanying MRCI additional instructions document.34 Akin to the suggestions of Abou-Karam et al.,29 if recommendations in the MRCI additional instructions were different from those described in the original MRCI article,3 scoring was conducted in accordance with the latter. For situations where no guidance for scoring was provided in either MRCI additional instructions or the original MRCI article, working guidelines were developed by the authors (MRCI weighting score of 3 for Respimat© and continuous positive airway pressure).

Statistical analysis
Data were analyzed using Stata 13 (StataCorp LP, College Station, TX, USA) and were reported as mean (SD) or median (interquartile range [q1, q3]) depending on the distribution. Wilcoxon rank-sum test was used to compare medication counts, total MRCI scores, and MRCI sub-scores between COPD and non-COPD medications. Comparison of categorical data was performed using Fisher’s exact test. Spearman’s rank correlation coefficient was used to examine the associations of medication count and regimen complexity with clinical outcomes and multidimensional indices. The differences in total medication counts and total MRCI scores for all medications in patients with and without a given class of comorbidity were assessed using either Student’s t-test (for normally distributed data) or Wilcoxon rank-sum test (for skewed data). Using the class of comorbidities that resulted in statistically significant differences in medication counts or MRCI scores in the abovementioned comparison analyses, we performed multiple regression analyses, adjusting for age and sex, to identify which classes of comorbidities individually contributed to higher medication counts and complex medication regimens. Prior to fitting the regression models, multicollinearity of variables was assessed using the variance inflation factor (VIF), which measures how much the variance of an estimated regression coefficient increases if predictors are correlated. A VIF score of between 5 and 10 is often taken as an indication that multicollinearity may be overly influencing the least squares estimates.35 Kruskall–Wallis test was performed to compare medication counts and MRCI scores in patients grouped in the different GOLD grades and quadrants. All results were reported as significant when \( P<0.05 \).

Results
Cohort characteristics
Participants (58.6% males) had a mean (SD) age of 69.1 (8.3) years and mild-to-severe airflow limitation (Table 1). Over one-third (38%) of participants were GOLD grade 3 or higher, and over half (52.7%) were in GOLD quadrant D. Participants had significantly impaired health-related quality of life, with mean (SD) CAT and SGRQ scores of 20.6 (6.9) and 54.1 (16), respectively.

Comorbidities
A total of 118 comorbidities were recorded. The number of comorbidities per participant ranged from 0 to 11 with a median \((q1, q3)\) of 5 (3, 7). Figure 1 shows the prevalence of comorbidities by disease categories. The prevalence of individual comorbidities is provided in Table S1.

Medication count and MRCI
Table 2 presents medication counts and MRCI scores. The percentage contributions of dosage form (section A), dosing frequency (section B), and dosage instructions (section C) to the total MRCI scores of COPD, non-COPD, and all medications are shown in Figure 2. The median \((q1, q3)\) total MRCI...
Table 1: Demographics and clinical characteristics of cohort

| Characteristic                  | Value (n=222) |
|--------------------------------|---------------|
| Sex (male)                     | 130 (58.6%)   |
| Age (years)                    | 69.1 (8.3)    |
| BMI (kg/m²)                    | 30.5 (24.5, 35.4) |
| Postbronchodilator FEV₁ (% predicted) | 56.5 (20.4) |
| Postbronchodilator FVC (% predicted) | 76.9 (17.2) |
| FEV₁/FVC ratio                 | 55 (16.3)     |
| mMRC score ≥ 2                 | 167 (75.2%)   |
| GOLD grades                    |               |
| I                              | 29 (13%)      |
| 2                              | 107 (48.2%)   |
| 3                              | 63 (28.4%)    |
| 4                              | 23 (10.4%)    |
| GOLD quadrant                   |               |
| A                              | 21 (9.5%)     |
| B                              | 49 (22%)      |
| C                              | 35 (15.8%)    |
| D                              | 117 (52.7%)   |
| Smoking status                 |               |
| Ex-smokers                     | 197 (88.7%)   |
| Smokers                        | 6 (2.7%)      |
| Never smokers                  | 19 (8.6%)     |
| Pack-years                     | 40 (21, 62)   |
| CAT score (n=190)              | 20.6 (6.9)    |
| SGRQ (n=217)                   | 54.1 (16)     |
| HADS total score (n=221)       | 12 (7, 16)    |
| Exacerbation history           | 2 (1, 3)      |
| 6MWD meters (n=156)            | 382.9 (275, 454.6) |
| Current respiratory medication use |                |
| SABA                           | 206 (92.8%)   |
| LABA                           | 28 (12.6%)    |
| SAMA                           | 11 (5%)       |
| LAMA                           | 194 (87.4%)   |
| Theophylline                   | 4 (1.8%)      |
| ICS                            | 24 (10.8%)    |
| ICS/LABA combination           | 179 (81%)     |
| OCS                            | 3 (1.4%)      |
| LTRA                           | 2 (0.9%)      |
| Oxygen                         | 19 (8.6%)     |
| Nasal steroids                 | 8 (3.6%)      |
| Indices                        |               |
| Comorbidity-specific indices   |               |
| CCI                            | 4 (3, 5)      |
| COTE (n=150)                   | 1 (0, 3)      |
| CODEx                          | 3 (2, 5)      |
| Multidimensional indices       |               |
| BODE (n=156)                   | 3 (1, 5)      |
| BODEx                          | 3 (2, 5)      |
| ADO                            | 4.7 (1.7)     |
| DOSE                           | 2.7 (1.6)     |

Note: Data presented as n (%), mean (SD), or median (interquartile range [q₁, q₃]).

Abbreviations: ADO, age, dyspnea and airflow obstruction; BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnea and exercise capacity; BODEx, body mass index, airflow obstruction, dyspnea and severe exacerbation; CCI, Charlson Comorbidity Index; CODEx, comorbidity, airway obstruction, dyspnea and severe exacerbation; COTE, comorbidity test; DOSE, dyspnea, airflow obstruction, smoking status and exacerbation; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HADS, hospital anxiety and depression scale; ICS, inhaled corticosteroids; LABA, long-acting beta₂ agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; 6MWD, 6-minute walk distance; mMRC, modified Medical Research Council; OCS, oral corticosteroids; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; SGRQ, St George’s Respiratory Questionnaire.

Comparisons of medication counts and regimen complexity based on GOLD quadrants and GOLD grades

When considering all medications, participants in GOLD quadrant D had significantly higher total MRCI score compared to those in quadrant A (P=0.0004) (Figure 3). With regard to COPD-specific medications, participants in GOLD quadrant D had significantly higher total MRCI scores compared to those in GOLD quadrants A (P=0.0001) and B (P<0.0001) (Figure 3). Furthermore, both sections A (dosage form) and B (dosing frequency) sub-scores of the total MRCI score of COPD medications were significantly higher for participants in GOLD quadrant D (10 [7, 10] versus 2 [1, 3], respectively; P<0.0001) (Table 2). MRCI section A sub-score (dosage form) was the greatest contributor to total MRCI score of COPD medications accounting for 62.1% (Figure 2) and was significantly greater than that for non-COPD medications (9 [7, 10] versus 2 [1, 3], respectively; P<0.0001) (Table 2). MRCI section A quantifies complexity associated with using different dosage forms and may serve as a measure of inhaler device polypharmacy for the COPD medications we considered. In this study, 68 (30.6%) participants had three or more different inhaler devices prescribed concurrently. In the case of non-COPD medications, MRCI section B sub-score (dosing frequency) primarily drove the total MRCI score accounting for 66.7% (Figure 2).
Table 2 Summary of MrCI and medication count for study population

| Measures                               | All medications | COPD medications | Non-COPD medications | P-value* |
|----------------------------------------|-----------------|------------------|-----------------------|----------|
| Total number of medications           | 8 (6, 11)       | 3 (3, 4)         | 5 (3, 8)              | <0.0001  |
| MrCI section A score (dosage form)    | 11 (8, 12)      | 9 (7, 10)        | 2 (1, 3)              | <0.0001  |
| MrCI section B score (frequency)      | 10 (7.5, 14.5)  | 3.5 (3.5, 5.5)   | 6 (3.5, 9)            | <0.0001  |
| MrCI section C score (direction)      | 3 (2, 5)        | 2 (1, 2)         | 1 (0, 3)              | 0.0188   |
| Total MrCI score                      | 24 (18.5, 31)   | 14.5 (11.5, 17.5)| 9 (5.5, 15)           | <0.0001  |

Notes: Data presented as median (q1, q3). *P-value for the comparison of COPD and non-COPD medications.
Abbreviation: MrCI, medication regimen complexity index.

our analysis also showed that participants in GOLD grade 4 were taking significantly higher number of COPD medications (median 4 [3, 4]) compared to those in GOLD grades 1 (median 3 [2, 3]; P<0.0001) and 2 (median 3 [2, 3]; P=0.0002). In addition, participants in GOLD grades 4 (median MRCI 18 [13.5, 21]) and 3 (median MRCI 15.5 [12.5, 19.5]) were found to have more complex COPD medication regimens than their counterparts in GOLD grades 1 (median MRCI 12.5 [9.5, 15.5]; P<0.0001) and 2 (median MRCI 13.5 [11, 15.5]; P=0.0002). The associations between medication burden and COPD outcomes

There was a weak but significant positive association between total MrCI score for all medications and CAT score, SGRQ, and prior year exacerbation history (Table 3). We found a significant negative association between total MrCI score for all medications and 6-minute walk distance (6MWD). There were weak but significant positive relationships between total medication count for all medications and SGRQ and exacerbation history in the previous 12 months. Total medication counts negatively correlated with 6MWD. In contrast, we found no significant relationship between total medication counts and CAT score (Table 3). Both total MrCI score and total medication counts for all medications (ie, COPD and non-COPD medications together) did not show any correlations with postbronchodilator FEV1% predicted and prior year hospitalization history.

With regard to COPD-specific medications, significant but weak positive correlations were found between total MrCI score for COPD drugs and CAT score, SGRQ, and preceding year exacerbation and hospitalization history. Increased complexity of COPD-specific treatments showed weak correlations with lower lung function and 6MWD (Table 3). Similarly, SGRQ, CAT score, and number of exacerbations in the previous 12 months correlated positively with the number of COPD medications. In contrast, correlation between number of COPD medications and number of hospitalizations in the previous 12 months was absent. Higher number of COPD medications correlated with lower lung function and 6MWD (Table 3).

Medication counts and regimen complexity in relation to class of comorbidities

In our study, total medication count for all medications was significantly higher for participants with comorbid cardiovascular diseases, gastrointestinal diseases, musculoskeletal conditions, metabolic disorders, respiratory diseases, psychiatric disorders, skin disorders, or neurological conditions compared...
to those without these conditions. Comorbid cancer did not contribute to higher total medication counts (Table 4).

With regard to medication regimen complexity, our preliminary analysis has shown that participants with comorbid cardiovascular diseases, gastrointestinal diseases, metabolic disorders, other respiratory conditions, psychiatric disorders, or neurological conditions tended to have significantly higher total MRCI scores for all medications compared to those without these conditions (Table 4). Further examination revealed that non-COPD medications primarily drove medication complexity in the cases of comorbid cardiovascular diseases, gastrointestinal diseases, other respiratory conditions, or neurological conditions (Figure 4A). In contrast, both COPD and non-COPD medications significantly contributed to complex medication regimens in the cases of comorbid metabolic or psychiatric disorders (Figure 4B). Comorbid musculoskeletal diseases, skin disorders, and cancer did not contribute to complex medication regimen.

In order to identify which categories of comorbid conditions individually contributed to higher medication counts or greater complexity of regimen, multiple regression analyses were performed with either total medication counts or total MRCI score for all medications as dependent variables, after adjusting for age and sex. Accordingly, cardiovascular diseases (β=2.381; 95% confidence interval [CI]: 1.360–3.403; P<0.0001), gastrointestinal diseases (β=0.927; 95% CI: 0.014–1.841; P=0.047), and metabolic disorders (β=1.003; 95% CI: 0.068–1.939; P=0.036) were found to be the three classes of comorbidities that significantly contributed to higher total medication counts. The proportion of variance

## Table 3 Correlations between clinical outcomes and medication burden

| Clinical outcomes                        | Total MRCI score for all medications | Total medication counts | COPD-specific medications MRCI score | COPD-specific medication count |
|-----------------------------------------|--------------------------------------|-------------------------|--------------------------------------|-------------------------------|
| CAT score                               | r=0.211; P=0.0034                     | p=0.132; P=0.0697       | p=0.200; P=0.0056                   | p=0.195; P=0.0070            |
| SGRQ                                    | r=0.301; P<0.0001                     | p=0.235; P=0.0005       | p=0.294; P<0.0001                   | p=0.299; P<0.0001            |
| Postbronchodilator FEV₁ (% predicted)   | r=-0.106; P=0.1141                   | p=0.071; P=0.2907       | p=-0.393; P<0.0001                 | p=-0.408; P<0.0001          |
| Prior year exacerbation history         | r=0.213; P=0.0014                     | p=0.133; P=0.0486       | p=0.246; P=0.0002                   | p=0.276; P<0.0001           |
| Prior year hospitalization history      | r=0.109; P=0.1043                     | p=0.095; P=0.1583       | p=0.151; P=0.0249                   | p=0.130; P=0.0528           |
| 6MWD                                    | r=0.369; P<0.0001                     | p=0.302; P<0.0001       | p=-0.288; P=0.0003                  | p=-0.259; P=0.0011          |

**Abbreviations:** CAT, COPD assessment test; FEV₁, forced expiratory volume in 1 second; 6MWD, 6-minute walk distance; MRCI, medication regimen complexity index; SGRQ, St George’s Respiratory Questionnaire.
explained by the regression model of total medication count \( (R^2) \) was 0.29 \( (P<0.0001) \) (Table 5). Cardiovascular diseases \( (\beta=3.225; 95\% \text{ CI: } 0.565–5.885; P=0.018) \) were the only class of comorbidities that individually contributed to the regression model of medication complexity (overall model fit \( [R^2]=0.18; P<0.0001 \) ) (Table 6).

### Associations between medication burden and clinical scores in COPD

The correlations between total MRCI score for all medications and each of the following multidimensional indices CCI, COTE, CODEx, BODE, BODEx, DOSE, and ADO, as well as total medication count and the before mentioned indices are summarized in Table 7. The comorbidity-specific indices CCI and COTE showed the highest degree of correlation with both total MRCI score and medication counts. Total MRCI score was significantly associated with each of the remaining five indices considered, whereas medication count was only weakly associated with CODEx.

### Discussion

The present study set out to explore the associations of medication burden, as measured by medication count and MRCI, with clinical outcomes, comorbidities, and clinical scores in COPD. While similar previous studies in COPD mainly investigated the relationships between medication count and clinical outcomes only, to the best of our knowledge, the present study is the first to describe the relationships of COPD outcomes, comorbidities, and multidimensional indices with medication burden beyond medication count.

Our findings have shown that complex medication regimens are associated with COPD disease severity and specific class of comorbidities. According to our data, COPD medication counts and regimen complexity significantly related to both GOLD grades and GOLD quadrants. For instance, participants in GOLD grades 4 (median MRCI 18) and 3...
Higher usage of nebulizer (MRCI weightings: 5) or oxygen (MRCI weightings: 3) in participants in GOLD quadrant D (Table S2) may have partly contributed to the aforementioned complexity of COPD-specific regimens in this group, as they are among the least convenient dosage forms due to the relative degree of difficulty in their administrations.5 In contrast, while no single dosing frequency was able to individually account for the higher MRCI section B score in patients in GOLD quadrant D, the combined higher occurrences of three times daily, four times daily, every 6 hours, and oxygen use over 15 hours may partly be responsible. Of note, the use of pressurized metered-dose inhaler with a spacer for bronchodilator therapy has been shown to be as effective as nebulizer therapy, at least in acute asthma.38 In relation to this, the findings of the present study demonstrate how nebulizers increase complexity of medication regimens and add support to the conversion of therapy to inhaler devices. It is worth mentioning here that long-term noninvasive ventilation (NIV) is increasingly being employed in COPD patients, particularly in those with pronounced hypercapnia.39 Unfortunately, however, data on the use of home NIV were not collected in our study. The absence of this data may potentially underestimate the overall burden of treatment, especially in the case of the severe COPD patients.

Our data also demonstrate significant but weak correlations of poor lung function, poor 6MWD, impaired health-related quality of life, and higher number of prior year exacerbations with both higher number and increased

### Table 5 Results of multiple regression analysis for comorbidities that contributed to higher medication count

| Model                        | Coefficient | t     | Significance | 95% confidence interval |
|------------------------------|-------------|-------|--------------|-------------------------|
| Constant                     | 5.284       | 11.50 | <0.0001      | (4.378, 6.190)          |
| Cardiovascular diseases      | 2.381       | 4.590 | <0.0001      | (1.360, 3.403)          |
| Gastrointestinal diseases    | 0.927       | 2.000 | 0.047        | (0.014, 1.841)          |
| Musculoskeletal diseases     | 0.149       | 0.340 | 0.737        | (-0.725, 1.024)         |
| Metabolic disorder           | 1.003       | 2.110 | 0.036        | (0.068, 1.939)          |
| Other respiratory diseases   | 0.621       | 1.370 | 0.171        | (-0.270, 1.512)         |
| Psychiatric disorders        | 0.681       | 1.500 | 0.134        | (-0.211, 1.574)         |
| Skin disorders               | 0.376       | 0.800 | 0.425        | (-0.551, 1.303)         |
| Neurological conditions      | 0.912       | 1.710 | 0.089        | (-0.140, 1.964)         |

**Notes:** The proportion of the variance explained by the model (R²) was 0.29; P<0.0001.

### Table 6 Results of multiple regression analysis for comorbidities that contributed to greater complexity of medication regimen

| Model                        | Coefficient | t     | Significance | 95% confidence interval |
|------------------------------|-------------|-------|--------------|-------------------------|
| Constant                     | 15.015      | 3.04  | 0.003        | (5.288, 24.743)         |
| Cardiovascular diseases      | 3.225       | 2.39  | 0.018        | (0.565, 5.885)          |
| Gastrointestinal diseases    | 1.725       | 1.48  | 0.139        | (-0.565, 4.016)         |
| Metabolic disorder           | 2.403       | 1.96  | 0.051        | (-0.010, 4.817)         |
| Other respiratory diseases   | 1.924       | 1.63  | 0.105        | (-0.406, 4.254)         |
| Psychiatric disorders        | 1.997       | 1.66  | 0.099        | (-0.376, 4.369)         |
| Neurological conditions      | 2.452       | 1.78  | 0.076        | (-0.259, 5.162)         |

**Notes:** The proportion of the variance explained by the model (R²) was 0.18; P<0.0001.
Table 7 Association of medication burden with comorbidity specific and multidimensional indices in COPD

| Indices                | Total MRCI score for all medications | Total medication count |
|------------------------|--------------------------------------|------------------------|
| Comorbidity-specific indices |                                      |                        |
| CCI                    | $\rho=0.289; P<0.0001$                | $\rho=0.359; P<0.0001$ |
| COTE                   | $\rho=0.326; P<0.0001$                | $\rho=0.316; P<0.0001$ |
| CODEx                  | $\rho=0.269; P<0.0001$                | $\rho=0.152; P=0.0240$ |
| Multidimensional indices |                                      |                        |
| BODE                   | $\rho=0.181; P=0.0237$                | $\rho=0.064; P=0.4257$ |
| BODEx                  | $\rho=0.198; P=0.0030$                | $\rho=0.061; P=0.3668$ |
| DOSE                   | $\rho=0.235; P=0.0004$                | $\rho=0.111; P=0.0988$ |
| ADO                    | $\rho=0.188; P=0.0049$                | $\rho=0.131; P=0.0509$ |

Abbreviations: ADO, age, dyspnea and airflow obstruction; BODE, body mass index, airflow obstruction, dyspnea and exercise capacity; BODEx, body mass index, airflow obstruction, dyspnea and severe exacerbation; CCI, Charlson Comorbidity Index; CODEx, comorbidity, airway obstruction, dyspnea and previous severe exacerbation; COTE, comorbidity test; DOSE, dyspnea, airflow obstruction, smoking status and exacerbation; MRCI, medication regimen complexity index.

The complexity of COPD-specific treatments. Similar associations between several clinical outcomes, including 6MWD, SGRQ score, and number of exacerbations in the previous 12 months with the number of respiratory medications in COPD patients, have been previously reported.17

Consistent with previous reports of Divo et al17 and Vanfleteren et al,44 participants in our study had a median of 5 (3, 7) comorbidities. As might be expected, the presence or absence of comorbid conditions can considerably influence the number of medications that patients take as well as the complexity of regimens.12 Most but not all of the comorbidities we studied were found to relate to overall medication burden in COPD. Our results illustrated that having comorbid musculoskeletal diseases, skin disorders, or cancer may not lead to a more complex pharmacotherapy in COPD patients. One possible explanation for this finding could be that these comorbidities may have been managed surgically and/or by using other non-pharmacological approaches (eg, radiation therapy and physiotherapy), the treatment burden of which cannot be captured by MRCI. In contrast, total MRCI score for all medications was significantly higher for patients with comorbid cardiovascular diseases, gastrointestinal diseases, metabolic disorders, other respiratory conditions, psychiatric disorders, or neurological conditions compared to those without these conditions. Multiple regression analysis, with age and sex as confounding variables, revealed that the presence of a comorbid cardiovascular disease can contribute approximately two additional medications to total medication counts and lead to an increase in total MRCI score of 3.23. Conversely, all the remaining comorbidities failed to individually contribute to the total MRCI score and medication count with the exception of gastrointestinal diseases and metabolic disorders, which individually contributed one medication each to total medication counts. It should be noted here that only 18% of the variance in total MRCI score was explained by the regression model of medication complexity (Table 6), suggesting that other factors probably also contribute, for instance, the effects of two or more concurrently existing comorbidities. It would be worthwhile to further explore how the co-occurrence of different types of comorbidities could potentially impact the complexity of pharmacotherapy in COPD.

In this study, we identified a weak relationship between medication regimen complexity and some of the currently available multidimensional indices that are widely used for the assessment or prognostication of COPD and its comorbidities (Table 7). Multidimensional indices are important in the management of COPD due to their ability to stratify and prognosticate.41 Despite this, however, they have not been widely used outside the research setting. With this in mind, one of the objectives of this study was to determine whether MRCI (and/or medication count) could serve as alternative tool(s) that can easily be applied in clinical settings, given that clinicians routinely review patient’s medications in their day-to-day practice. While MRCI related to multidimensional indices in our study, the strength of the relationships we observed would not justify the use of MRCI or medication count in place of the existing multidimensional indices. Nevertheless, as in the case of related previous studies,12,13 the present study has illustrated that MRCI is a valuable clinical tool that can provide an insight into several aspects of disease and medication burden, which can form the basis for informed decision making and comprehensive medication review.

It is interesting to note that participants in our study were taking a higher number of medications compared to...
both slightly younger (median 62.7 [61.7, 63.8] years) and older (mean [SD] 73.7 [8.9] years) COPD patients in other studies. In our cohort, the median total MRCI score for all medications was 24 (18.5, 31). This relatively high MRCI score is similar to what previous studies reported in people with COPD (mean [SD] 28.7 [5]) and other chronic diseases including geriatric depression (mean [SD] 25.4 [11.7]), diabetes mellitus (mean [SD] 23 [11.6]), chronic kidney disease (mean [SD] 22.4 [10.2]), and HIV (median 21 [12, 29]) but lower than that reported in hospitalized COPD patients (mean [SD] 35.3 [14.4]) and elderly inpatients (≥65 years, mean [SD] 30.3 [14]).

We found that COPD-specific medication regimens were significantly more burdensome than those of non-COPD medications despite the fact that patients were taking a fewer number of COPD medications compared to non-COPD ones. COPD medication complexity was largely driven by complex dosage formulations (Figure 2). The concurrent use of multiple different types of inhaler devices was prevalent in our study population with one out of three patients having inhaler device polypharmacy (IDP) (defined as the use of three or more different inhaler devices). In people with respiratory diseases, complex medication regimens and IDP could lead to unintentional nonadherence to treatment, suboptimal device technique, and poor disease control. IPD is a recognizable attribute of airways disease that can be rectified via medication review and device rationalization.

Our findings suggest that MRCI is a tool that can potentially assist clinicians in this regard by serving as a risk assessment tool for identifying COPD patients who may benefit from simplification of a complex dosage regimen as originally intended by George et al.

Conclusion
This study illustrated that patients with COPD face dual disadvantages with medication regimen complexity as a result of, first, the complex dosage formulations of their COPD medications and, second, the multiple dosing frequencies of non-COPD medications they may take for their comorbid diseases. Clinicians need to carefully consider all aspects of the disease burden of COPD patients together with the multiple aspects of their pharmacotherapy to identify ways of reducing medication regimen complexity in order to improve treatment adherence, achieve better treatment outcomes, and reduce potential adverse drug events. Based on our findings, minimizing multiple dosing frequencies where possible, minimizing the use of nebulizers, reevaluating the use of inhaler devices, and/or opting for combination therapies can be suggested as ways of reducing the considerable burden of treatment in COPD patients. Future studies in this area could benefit from investigating the effects of modifying medication regimen complexity on clinically relevant outcomes such as adherence, patient satisfaction, health status, unplanned hospitalization, and adverse drug events.

One of the important findings of the present study was that comorbidities play a significant role in driving medication complexity in COPD. Given that COPD patients commonly suffer from multiple comorbidities, the relative significance of individual comorbidities and their co-occurrences on medication regimen complexity in COPD deserves further investigation.

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## Supplementary materials

### Table S1 Prevalence of self-reported diagnosed comorbidities

| Comorbidity                                      | Prevalence |
|--------------------------------------------------|------------|
| Cardiovascular diseases                          |            |
| Hypertension                                     | 91 (41%)   |
| Coronary artery disease                          | 21 (9.5%)  |
| Atrial fibrillation                              | 21 (9.5%)  |
| Arrhythmia/bundle branch blocks                  | 18 (8.1%)  |
| Ischemic heart disease                           | 14 (6.3%)  |
| Myocardial infarction                            | 11 (4.9%)  |
| Aortic valve disorders                           | 10 (4.5%)  |
| Congestive heart failure                         | 5 (2.3%)   |
| Stroke                                           | 4 (1.8%)   |
| Abdominal aortic aneurysm                        | 3 (1.4%)   |
| Low blood pressure                               | 2 (0.9%)   |
| Deep vein thrombosis                             | 2 (0.9%)   |
| Peripheral vascular disease                      | 1 (0.5%)   |
| Other respiratory diseases                       |            |
| Asthma                                           | 79 (35.6%) |
| Obstructive sleep apnea                          | 26 (11.7%) |
| Bronchiectasis                                   | 15 (6.8%)  |
| Pulmonary hypertension                           | 4 (1.8%)   |
| Asbestosis                                       | 4 (1.8%)   |
| Pulmonary embolism                               | 2 (0.9%)   |
| Pulmonary fibrosis                               | 1 (0.5%)   |
| Gastrointestinal diseases                        |            |
| Gastroesophageal reflux disease                  | 93 (41.9%) |
| Gastric/duodenal ulcer                           | 13 (5.9%)  |
| Hernia                                           | 10 (4.5%)  |
| Diverticulitis                                   | 8 (3.6%)   |
| Gall bladder removed                             | 5 (2.3%)   |
| Inflammatory bowel syndrome                      | 4 (1.8%)   |
| Ulcerative colitis                               | 1 (0.5%)   |
| Crohn’s disease                                  | 1 (0.5%)   |
| Metabolic disorders                              |            |
| Hyperlipidemia                                   | 72 (32.4%) |
| Diabetes                                         | 36 (16.2%) |
| Osteoporosis                                     | 24 (10.8%) |
| Hypothyroidism                                   | 15 (6.8%)  |
| Glucose intolerance                              | 5 (2.3%)   |
| Hyperthyroidism                                  | 2 (0.9%)   |
| Psychiatric disorders                            |            |
| Depression                                       | 68 (30.6%) |
| Anxiety                                          | 34 (15.3%) |
| Psychosis                                        | 2 (0.9%)   |
| Bipolar                                          | 1 (0.5%)   |
| Adjustment disorder                              | 1 (0.5%)   |
| Cancer                                           |            |
| Skin cancer                                      | 16 (7.2%)  |
| Prostate cancer                                  | 5 (2.3%)   |
| Breast cancer                                    | 5 (2.3%)   |
| Leukemia                                         | 4 (1.8%)   |
| Tumor on ENT                                     | 3 (1.4%)   |
| Ductal cell carcinoma                            | 1 (0.5%)   |
| Cervical cancer                                  | 1 (0.5%)   |
| Meningioma                                       | 1 (0.5%)   |
| (Continued)                                       |            |

### Table S1 (Continued)

| Comorbidity                                      | Prevalence |
|--------------------------------------------------|------------|
| Musculoskeletal diseases                         |            |
| Arthritis                                        | 52 (23.4%) |
| Osteoarthritis                                   | 40 (18.0%) |
| Osteopenia                                       | 3 (1.4%)   |
| Joint issues/fibromyalgia                        | 2 (0.9%)   |
| Blood disorders                                  |            |
| Anemia                                           | 14 (6.3%)  |
| Iron/vitamin B or D deficiency                   | 3 (1.4%)   |
| Hemochromatosis                                  | 2 (0.9%)   |
| Thrombocytopenia                                 | 1 (0.5%)   |
| High white blood cell count                      | 1 (0.5%)   |
| Pseudo-von Willebrand disease                    | 1 (0.5%)   |
| Urology                                          |            |
| Reduced kidney function                          | 14 (6.3%)  |
| Incontinence                                     | 12 (5.4%)  |
| Benign prostate hypertrophy                      | 10 (4.5%)  |
| Kidney infection                                 | 10 (4.5%)  |
| Gout                                             | 6 (2.7%)   |
| Kidney stone/hematuria                           | 6 (2.7%)   |
| Renal failure                                    | 4 (1.8%)   |
| Frequent urination                               | 3 (1.4%)   |
| Prolapsed bladder                                | 1 (0.5%)   |
| Hyperuricemia                                    | 1 (0.5%)   |
| Leaky bowel                                      | 1 (0.5%)   |
| Hepatic and pancreatic                           |            |
| Liver dysfunction/abnormal LFT                   | 6 (2.7%)   |
| Fatty liver                                      | 5 (2.3%)   |
| Pancreatitis                                     | 2 (0.9%)   |
| Hepatitis                                        | 2 (0.9%)   |
| Liver cirrhosis                                  | 1 (0.5%)   |
| Abscess in bile duct                             | 1 (0.5%)   |
| Reproductive                                     |            |
| Ovarian cyst                                     | 3 (1.4%)   |
| Pelvic inflammatory disease                      | 2 (0.9%)   |
| Prolapsed cervix/uterus                          | 2 (0.9%)   |
| Vaginal lesion                                   | 1 (0.5%)   |
| ENT                                              |            |
| Hay fever                                        | 23 (10.4%) |
| Sinusitis                                        | 20 (9.0%)  |
| Other ENT                                        | 13 (5.9%)  |
| Nasal polyps                                     | 6 (2.7%)   |
| Vocal cord dysfunction                           | 6 (2.7%)   |
| Rhinitis                                         | 5 (2.3%)   |
| Eye diseases                                     |            |
| Cataract                                         | 58 (26.1%) |
| Glaucoma                                         | 3 (1.4%)   |
| Astigmatism                                      | 2 (0.9%)   |
| Macular degeneration                             | 2 (0.9%)   |
| Retinal detachment                               | 2 (0.9%)   |
| Retinal vein thrombosis                          | 1 (0.5%)   |
| Neurological conditions                          |            |
| Headache                                         | 11 (5.0%)  |
| Transient ischemic attack                        | 11 (5.0%)  |
| Other neurological conditions                    | 10 (4.5%)  |
| Migraine                                         | 8 (3.6%)   |
| Tremors                                          | 4 (1.8%)   |

(Continued)
Table S1  (Continued)

| Comorbidity                          | Prevalence |
|--------------------------------------|------------|
| Sciatica                             | 3 (1.4%)   |
| Dementia                             | 3 (1.4%)   |
| Stenosis                             | 2 (0.9%)   |
| Motor neuron disease                 | 1 (0.5%)   |
| Epilepsy                             | 1 (0.5%)   |
| Bulged disc                          | 1 (0.5%)   |
| Cerebral abscess                     | 1 (0.5%)   |
| Skin disorders                       |            |
| Sciatica                             | 3 (1.4%)   |
| Dementia                             | 3 (1.4%)   |
| Stenosis                             | 2 (0.9%)   |
| Motor neuron disease                 | 1 (0.5%)   |
| Epilepsy                             | 1 (0.5%)   |
| Bulged disc                          | 1 (0.5%)   |
| Cerebral abscess                     | 1 (0.5%)   |
| Venous diseases                      |            |
| Varicose vein                        | 2 (0.9%)   |

**Abbreviations:** ENT, ear, nose and throat; LFT, liver function test.

Table S2 Use of nebulizer or oxygen in participants in different GOLD quadrants

| Nebulizer or oxygen use | GOLD quadrant A | GOLD quadrant B | GOLD quadrant C | GOLD quadrant D | Total |
|-------------------------|-----------------|-----------------|-----------------|-----------------|-------|
| No                      | 20              | 44              | 33              | 87              | 184   |
| Yes                     | 1               | 5               | 2               | 30              | 38    |
| Total                   | 21              | 49              | 35              | 117             | 222   |

**Note:** Fischer’s exact =0.005.

**Abbreviation:** GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table S3 Medication counts and MRCI scores of COPD, non-COPD, and all medications in GOLD quadrants

| Measures                              | GOLD quadrants | P-value |
|---------------------------------------|----------------|---------|
|                                      | A              | B       | C       | D       |
| COPD-specific medication count        | 3 (2, 3)       | 3 (2, 3)| 3 (3, 4)| 3 (3, 4)| 0.187 |
| Non-COPD medication count             | 4 (2, 7)       | 6 (4, 8)| 5 (3, 6)| 5 (3, 8)| 0.119 |
| Total medication count                | 6 (4, 10)      | 9 (6, 11)| 8 (6, 9)| 8 (6, 11)| 0.173 |
| MRCI score for COPD-specific medications | 13.5 (9.5, 15) | 12.5 (9.5, 15.5)| 13 (11.5, 16)| 15.5 (12.5, 19.5)| 0.0001 |
| MRCI score for non-COPD medications   | 8 (3, 14)      | 10 (7, 16)| 9 (5, 11)| 9 (5, 14)| 0.203 |
| MRCI score for all medications       | 22.5 (16, 26)  | 22.5 (18.5, 27.5)| 21.5 (19, 25)| 27 (19.5, 32.5)| 0.019 |

**Notes:** *P=0.0001 versus patients in GOLD A. **P=0.001 versus patients in GOLD A. ***P=0.004 versus patients in GOLD A.

**Abbreviations:** GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRCI, medication regimen complexity index.