Low Use and Adherence to Maintenance Medication in Chronic Obstructive Pulmonary Disease in the General Population

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OBJECTIVE: We tested the hypothesis that use of and adherence to maintenance medication is low among individuals in the general population who have chronic obstructive pulmonary disease (COPD), even in cases of severe and very severe COPD.

DESIGN AND PARTICIPANTS: We identified 5,812 individuals with COPD from the Copenhagen General Population Study, and classified them according to the Global Initiative for Obstructive Lung Disease (GOLD) airflow limitation grades 1–4. Dispensing of fixed-dose combinations of inhaled corticosteroids with long-acting beta₂-agonists, long-acting anti-cholinergics, or long-acting beta₂-agonists was identified in a nationwide registry. Use of medication was defined as medication dispensed during a one-year period, and adherence was calculated from dosages available in one year.

KEY RESULTS: Use of fixed-dose combinations of inhaled corticosteroids with long-acting beta₂-agonists varied from 2 % to 61 % ($p < 0.001$, test for trend), long-acting anti-cholinergics varied from 0.4 % to 36 % ($p < 0.001$), and long-acting beta₂-agonists varied from 0.3 % to 11 % ($p < 0.001$). Among utilizers of these medications, adherence varied from 29 % to 56 % ($p < 0.001$, test for trend) across GOLD 1–4 for fixed-dose combinations of inhaled

corticosteroids with long-acting beta₂-agonists, from 51 % to 68 % ($p = 0.11$) for long-acting anti-cholinergics, and from 25 to 62 % ($p = 0.01$) for long-acting beta₂-agonists.

CONCLUSIONS: Use of and adherence to maintenance medication for COPD in the general population was associated with the severity of COPD as defined by GOLD, but even in severe and very severe COPD, use and adherence was low.

KEY WORDS: COPD; severity; GOLD; long-acting medication.

ABBREVIATION

COPD	Chronic obstructive pulmonary disease
ICS/LABA	Fixed-dose combinations of inhaled corticosteroids with long-acting beta ₂ -agonists
LAMA	Long-acting anti-cholinergics
LABA	Long-acting beta ₂ -agonists
FEV ₁	Forced expiratory volume in one second
FVC	forced vital capacity
CGPS	Copenhagen General Population Study
GOLD	Global initiative for Obstructive Lung Disease

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What is the major question?

What are the patterns of use and adherence to maintenance medications according to severity of chronic obstructive pulmonary disease (COPD)?

What is important?

Individuals with COPD in the general population do not get the full benefits of maintenance medications, as these are often not used, and when they are used, adherence is low, even in severe and very severe COPD.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the major chronic diseases worldwide.¹ In randomized controlled trial settings, regular treatment with maintenance medication, including fixed-dose combinations of inhaled corticosteroids with long-acting beta₂-agonists (ICS/LABA), long-acting anti-cholinergics (LAMA), and long-acting beta₂-agonists (LABA), has been shown to improve symptoms, quality of life, and lung function, and to reduce the risk of exacerbations,

especially in those with severe and very severe COPD.^{2,3} However, even when prescribed, low adherence to these maintenance medications among patients in the real world could offset the benefit reported in randomized controlled trials.

Undertreatment of COPD has been reported previously,⁴ and studies have indicated that adherence to medication in COPD is low in the general population. Nevertheless, most studies have relied only on pharmaceutical databases, and have had limited clinical information.^{5,6} As a consequence, most knowledge on use and adherence in relation to clinical information such as severity of COPD comes from randomized controlled trials.⁷ There is a need for population-based studies on use and adherence to investigate whether real-life treatment of COPD could be improved.⁸

We hypothesized that use and adherence to maintenance medications is low, even in severe and very severe COPD.

DESIGN AND PARTICIPANTS

Study Population

In this study we used data from an ongoing prospective cohort study, the Copenhagen General Population Study (CGPS),⁹ which follows randomly selected individuals from the suburbs of Copenhagen. We studied individuals with COPD who were examined between 2003 and 2008. A flow diagram of the cohort is provided in Fig. 1. The subgroup of individuals with COPD was identified based on the presence of airflow limitation defined as a ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) less than 0.7.¹⁰ Only pre-bronchodilator lung function measurements were available. After the examination, all participants in the CGPS with airflow limitation were advised to contact their general practitioners. In addition, a letter with the results of the pulmonary function tests was sent to the participants to be taken to their general practitioners. We only included individuals over 40 years of age, and we excluded individuals with self-reported asthma. This resulted in 5,812 individuals with COPD (see Fig. 1). These individuals were classified according to the Global Initiative for Obstructive Lung Disease (GOLD) level of airflow limitation as GOLD 1–4.¹⁰ In addition, as sensitivity analysis, individuals with COPD were further classified as GOLD A–D based upon the presence of breathlessness, airflow limitation, and previous exacerbations.¹⁰

Linkage to National Registers

Our study population was linked to the national Danish Register of Medicinal Product Statistics (DRMPS),¹¹ with all-

inclusive information on drugs dispensed (i.e., physically retrieved) at all Danish pharmacies from 1995 through December, 31, 2009. We analyzed complete data for maintenance medications recommended for treatment of COPD according to the GOLD recommendations¹⁰: fixed-dose combinations of inhaled corticosteroids with long-acting beta₂-agonists (ICS/LABA), long-acting anti-cholinergics (LAMA), and long-acting beta₂-agonists (LABA).^{2,3}

We also used linkage to the all-inclusive Danish National Patient Register¹² to identify hospital admissions for COPD (ICD-10: J41–44).

Use of Maintenance Medication

Use of maintenance medication was defined as at least one physically retrieved prescription of ICS/LABA, LAMA, or LABA within one year *after* the examination in the CGPS for each individual. We defined previous use of maintenance medication similarly, based on data for the year before the examination.

Adherence to Maintenance Medication

To calculate adherence, we used dispensed dosages of ICS/LABA, LAMA, and LABA in the first year after each individual's baseline examination. We calculated adherence in GOLD 1–4 as a fixed medication possession ratio¹³ according to available dosages for each class of maintenance medication in the following way:

$$\text{Adherence} = \frac{100\% * \text{dispensed quantity in the first year after examination}}{\text{recommended daily dosage} * 365.25}$$

Appendix-Table 1 (available online) shows the daily dosages of maintenance medications used to calculate adherence.^{14,15} Adherence >80 % was considered high adherence according to previous literature.⁷ Previous adherence was calculated for the year before the baseline examination.

Loss to Follow-up

Among 55 (0.9 %) individuals who died or emigrated during follow-up, five were users of maintenance medications. Their adherence was calculated using risk time in days (time from examination to death or emigration) rather than 365.25 days. The average risk time for these individuals was 142 days. This method avoids underestimating adherence.

SENSITIVITY ANALYSES

Due to the limited number of users with very severe COPD, we restricted three of every four sensitivity analyses by combining severe and very severe COPD (GOLD 3+4), to gain sufficient power in these analyses.

Figure 1. Individuals with COPD in the Copenhagen General Population Study. The figure shows a flow diagram deriving the subgroup of 5,812 individuals with COPD in this study, classified according to GOLD grades 1–4 (Global Initiative for Obstructive Lung Disease).

Use and Adherence in GOLD A–D

In the first sensitivity analysis, we classified individuals according to GOLD A–D severity,¹⁰ and calculated use and adherence in the first year after the examination in GOLD A–D.

Temporal Changes

In the second sensitivity analysis, we analyzed temporal trends in the use of maintenance medications by dividing our cohort into two equally sized subgroups; 2,876 individuals examined before June 30, 2006, and 2,936 individuals examined after June 30, 2006. We then compared usage during the first year after the examination for all maintenance medications in GOLD 1, GOLD 2, and GOLD 3+4 groups.

Adherence among Users of Only One Type of Maintenance Medication

Since some individuals could potentially switch or add on therapy during follow-up, adherence for these

individuals would be more difficult to interpret. Therefore, in a third sensitivity analysis, we calculated adherence among the subgroup of 383 users who used only one type of maintenance medication during follow-up.

Adherence in a One-Year Period from the First Dispensing

Because time until first dispensing of medication after the examination could affect our estimates of adherence, we calculated adherence in a period of one year from a user's first dispensed medication, including the first dispensed dosage. A subgroup of 496 users whose medication was first dispensed before December 31, 2008, was included in this fourth sensitivity analysis, ensuring one year of follow-up.

Study Approval

The study was approved by an institutional review board and the Danish ethics committee (H-KF01-144/

01), and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

STATISTICAL ANALYSIS

Use and Adherence

We used the statistical software package R (version 2.15.3) for all analyses.¹⁶ For comparison of the proportion of users across GOLD grades and for comparison of adherence across GOLD grades, we used tests for trend.^{16,17} To compare baseline demographics we used Chi-squared tests or ANOVA for categorical or continuous variables, as appropriate.¹⁷

Variables Associated with Adherence

Multivariable linear regression analyses were applied to examine which baseline variables were associated with adherence for ICS/LABA, LAMA and LABA during the first year after the examination. Since the evidence on beneficial effects of regular treatment with maintenance medications has been best described for COPD patients with an $FEV_1 < 60$ %, we restricted the multivariable analyses to this subgroup.^{2,3} In multivariable regression analyses we included variables associated with COPD including FEV_1 , smoking, previous exacerbations, chronic bronchitis, breathlessness, and physical activity in leisure time as possible confounders.¹⁰ In addition, we included variables possibly associated with adherence including comorbidity, age, gender, visits to the general practitioner, socioeconomic status, psychosocial variables, as well as the year of cohort entry.^{18–24} Appendix-Table 2 (available online) shows a detailed description of all variables.

Since previous adherence has been identified as a dominant predictor of future adherence in COPD,²⁵ we did a fifth sensitivity analysis that did not include previous adherence among possible explanatory variables in the models in order to investigate possible masking of other variables caused by collinearity.

Initial model selection was performed by the automated model simplification step-function in R using the Akaike information criterion. This method explicitly penalizes any unnecessary parameters in the models by adding two times the number of parameters to the deviance (the deviance information criterion, i.e., the hierarchical modeling generalization of the Akaike information criterion), thereby avoiding overfitting of data.¹⁷ P values less than 0.05 were considered statistically significant. Non-significant variables were tested individually and nested sub-models were tested against larger models using ANOVA.¹⁷ In this way, the most parsimonious model was selected as the final model. All P values reported are two-sided.

RESULTS

Demographics

Among 5,812 individuals with COPD in the Copenhagen General Population Study, 3,015 (51.9 %) had mild airflow limitation (GOLD 1), 2,422 (41.7 %) had moderate airflow limitation (GOLD 2), 339 (5.8 %) had severe airflow limitation (GOLD 3), and 36 (0.6 %) had very severe airflow limitation (GOLD 4). Table 1 shows baseline demographics according to GOLD grades 1–4.

Use and Adherence to Maintenance Medications

We identified 532 individuals (9.2 %) who were users of any type of maintenance medication (at least one maintenance medication), 455 users of any LABA (LABA and/or ICS/LABA), 388 users of ICS/LABA, 206 users of LAMA, and 96 users of LABA.

Across all maintenance medications, usage increased with the severity of COPD as defined by GOLD 1–4 ($p < 0.001$ for all medications), as shown in the left part of Fig. 2. In severe and very severe COPD (GOLD 3+4), ICS/LABA was the most frequently used maintenance medication, used by 33 %. However, use of any LABA was 39 % in severe and very severe COPD.

With the exception of LAMA, adherence increased significantly with progressive GOLD grades 1–4. However, no maintenance medication reached high average adherence for any GOLD groups, as shown in the right part of Fig. 2. High adherence (> 80 % adherence) was reached by 16 % (62/388) of ICS/LABA users, 33 % (68/206) of LAMA users, and 18 % (17/96) of LABA users.

SENSITIVITY ANALYSES

Use and Adherence in GOLD A–D

Among 5,812 individuals with COPD, 5,809 (99.9 %) had data that allowed grading according to GOLD A–D; 4,561 (78.5 %) were GOLD A, 786 (13.5 %) were GOLD B, 223 (3.8 %) were GOLD C, and 239 (4.1 %) were GOLD D. Use and adherence to maintenance medications was low for all GOLD A–D grades, but increased progressively with GOLD grades A–D. However, high average adherence was not reached in any group, as shown in Fig. 3.

Temporal Changes

In the second sensitivity analysis, we compared use of maintenance medications in two subgroups: 2003–2006

Table 1. Demographics of 5,812 individuals with chronic obstructive pulmonary disease (COPD) in the Copenhagen General Population Study. Graded according to GOLD 1–4 severity of COPD (Global Initiative for Obstructive Lung Disease grades 1–4 airflow limitation)

Variables	GOLD 1 (n=3,015)	GOLD 2 (n=2,422)	GOLD 3 (n=339)	GOLD 4 (n=36)	P value
Age in years - mean (SD)	66 (12)	66 (11)	70 (10)	68 (9)	<0.001
Breathlessness* - % (n/N)	9 (275/3,013)	22 (542/2,422)	52 (176/338)	89 (32/36)	<0.001
FEV ₁ % predicted - mean (SD)	95 (11)	68 (8)	43 (5)	25 (5)	<0.001
Males - % (n/N)	46 (1,374/3,015)	48 (1,173/2,422)	54 (183/339)	56 (20/36)	=0.008
Previous severe exacerbations† - % (n/N)	0.1 (2/3,015)	1 (20/2,422)	5 (16/339)	14 (5/36)	<0.001
Previous moderate exacerbations‡ - % (n/N)	2 (70/3,015)	3 (70/2,422)	11 (37/339)	17 (6/36)	<0.001
Comorbidity§	46 (1,377/3,015)	53 (1,295/2,422)	69 (234/339)	64 (23/36)	<0.001
Education<8 years - % (n/N)**	19 (570/2,998)	25 (595/2,407)	34 (114/337)	31 (11/36)	<0.001
Education 8–10 years - % (n/N)**	47 (1,423/2,998)	50 (1,195/2,407)	49 (164/337)	56 (20/36)	<0.001
Education>10 years - % (n/N)**	34 (1,005/2,998)	26 (617/2,407)	18 (59/337)	14 (5/36)	<0.001
Physical activity low (<2 h)††	6 (187/2,972)	12 (275/2,381)	20 (65/331)	22 (8/36)	<0.001
Physical activity intermediate (2–4 h) ††	44 (1,320/2,972)	53 (1,251/2,381)	53 (175/331)	53 (19/36)	<0.001
Physical activity high (>4 h) ††	49 (1,465/2,972)	36 (855/2,381)	28 (91/331)	25 (9/36)	<0.001
Current smokers - % (n/N)	30 (895/2,962)	46 (1,091/2,385)	50 (167/333)	32 (11/34)	<0.001
Previous use of ICS/LABA - % (n/N)	1 (42/3,015)	5 (113/2,422)	17 (59/339)	44 (16/36)	<0.001
Initiated ICS/LABA after examination - % (n/N)	1 (36/3,015)	5 (117/2,422)	15 (52/339)	22 (8/36)	<0.001
Stopped ICS/LABA after examination - % (n/N)	1 (16/3,015)	1 (29/2,422)	2 (8/339)	6 (2/36)	<0.001
Previous use of LAMA - % (n/N)	0.3 (10/3,015)	2 (56/2,422)	16 (53/339)	28 (10/36)	<0.001
Initiated LAMA after examination - % (n/N)	0.2 (5/3,015)	2 (58/2,422)	9 (31/339)	11 (4/36)	<0.001
Stopped LAMA after examination - % (n/N)	0.1 (2/3,015)	0.4 (9/2,422)	3 (9/339)	3 (1/36)	<0.001
Previous use of LABA - % (n/N)	0.1 (4/3,015)	1 (33/2,422)	9 (30/339)	8 (3/36)	<0.001
Initiated LABA after examination - % (n/N)	0.2 (5/3,015)	1 (28/2,422)	3 (10/339)	3 (1/36)	<0.001
Stopped LABA after examination - % (n/N)	0.0 (1/3,015)	0.3 (8/2,422)	3 (9/339)	0 (0/36)	<0.001

FEV₁ forced expiratory volume in one second, ICS/LABA fixed-dose combinations of inhaled corticosteroids with long-acting beta₂-agonists, LAMA long-acting anti-cholinergics, LABA long-acting beta₂-agonists

*A modified Medical Research Council scale score, mMRC≥2. †At least one discharge diagnosis of COPD within the last year **The education categories correspond to lower primary school, higher primary school and secondary school, or college and university in Denmark.²⁴

‡At least one treatment with oral corticosteroids alone or in combination with antibiotics within the last year. ††Leisure-time physical activity categories

§Comorbidity: previous self-reported deep venous thrombosis and/or pulmonary embolism, cardiovascular disease, CNS disease including cerebrovascular disease, diabetes, cancer, and/or reporting 'other chronic diseases'; see Appendix-Table 2 (available online) for further details

Fisher's exact test was used for low cell counts

versus 2006–2009. The only clinically relevant significant change was observed in severe and very severe COPD (GOLD 3+4), where we observed an increase in users of ICS/LABA from 27 % users in 2003–2006 to 43 % users in 2006–2009 ($p=0.002$).

Adherence among Users of Only One Type of Maintenance Medication

Studying the subgroup of 383 users (72 % of all users) who used only one type of maintenance medication, we observed very similar levels of adherence in our third

Figure 2. Use and adherence to maintenance medications in 5,812 individuals with chronic obstructive pulmonary disease (COPD) in the Copenhagen General Population Study. LEFT PART: the bars show the percentage of individuals in GOLD 1–4 that received at least one dispensed fixed-dose combination of inhaled corticosteroids with long-acting beta₂-agonists (ICS/LABA), long-acting anti-cholinergics (LAMA), or long-acting beta₂-agonists (LABA) in the year following the examination. The numbers adjacent to the bars show number of users/number in the corresponding GOLD group. P values show test for trend across GOLD 1–4. **RIGHT PART:** The bars show average adherence in one year calculated among users (the number of users is shown to the left of the bars). P values show test for trend across GOLD 1–4.

Figure 3. Use and adherence to maintenance medications in 5,809 individuals with chronic obstructive pulmonary disease (COPD) in the Copenhagen General Population Study. **LEFT PART:** the bars show the percentage of individuals in GOLD A–D that received at least one dispensed prescription of fixed-dose combinations of inhaled corticosteroids with long-acting beta₂-agonists (ICS/LABA), long-acting anticholinergics (LAMA), or long-acting beta₂-agonists (LABA) in the year following the examination. The numbers adjacent to the bars show number of users/number in the corresponding GOLD group. P values show test for trend across GOLD A–D. **RIGHT PART:** The bars show average adherence in one year calculated among users (the number of users is shown to the left of the bars). P values show test for trend across GOLD A–D.

sensitivity analysis as those reported in the main analysis; see Appendix-Fig. 1 (available online).

Adherence in One-Year Period from the First Dispensing

In the fourth sensitivity analysis, we calculated adherence from the first dispensing, including the first dispensed dosage, in a subgroup of 496 users. Adherence was similar to the results reported in our main analysis; see Appendix-Fig. 2 (available online).

Variables Associated with Adherence

Table 2 shows the multivariable models. Among 176 users of ICS/LABA, the variables of previous adherence, physical activity in leisure time, and comorbid condition were associated with increased adherence, while higher education was associated with decreased adherence (adjusted R-squared=0.49). Furthermore, among 136 users of LAMA, previous adherence was associated with increased adherence (adjusted R-squared=0.20). Finally, among 60 users of LABA, the variables of previous adherence and male gender were associated with increased adherence, while a high FEV₁ was associated with decreased adherence (adjusted R-squared=0.45).

The sensitivity analysis, without previous adherence among possible variables, confirmed that physical activity in leisure time and comorbidity were associated with increased adherence, and higher education was still associated with decreased adherence. However, a high FEV₁ was now included in all three models and was associated with decreased adherence (data not shown).

DISCUSSION

In this study, we observed that use and adherence to maintenance medications of fixed dose-combinations of inhaled corticosteroids with long-acting beta₂-agonists, long-acting anti-cholinergics, or long-acting beta₂-agonists in individuals with COPD in the general population were low, even in cases of severe and very severe COPD. To our knowledge, this is the first study of unselected individuals from the general population showing a strong association between GOLD 1–4 severity and use of and adherence to these maintenance medications, with the exception of adherence to LAMA. However, in GOLD A–D, we also found a significant association with severity of COPD for LAMA adherence.

Although use of medication was associated with severity of COPD, our results indicate that a large proportion of individuals with severe and very severe COPD in the general population seem to be undertreated. Despite increased adherence with progressive severity of COPD, adherence was low for all GOLD categories, even in severe and very severe COPD, and these observations may hamper generalization of beneficial results reported from randomized controlled trials to actual treatment of patients in the real world.^{2,3,7}

Temporal changes in prescribing habits could affect our estimates. However, we only observed clinically relevant significant temporal change for use of ICS/LABA that increased in severe and very severe COPD comparing 2003–2006 with 2006–2009. Still, even in 2006–2009, ICS/LABA was used by only 43 % in severe and very severe COPD.

Use of medication, defined by physically collecting at least one dispensed medication at the pharmacy, is easy to interpret, but there is no gold standard for analyzing adherence in pharmacoepidemiological studies.⁸ In this study, adherence was calculated as a fixed medication possession ratio,¹³ according to available dosages in the first year after the

Table 2. Multivariable analyses in individuals with COPD and FEV₁ <60 % showing variables associated with adherence among 176 users of ICS/LABA (fixed-dose combinations of inhaled corticosteroids with long-acting beta₂-agonists), 136 users of LAMA (long-acting anti-cholinergics), and 60 users of LABA (long-acting beta₂-agonists)

Variables	Adherence	
ICS/LABA	± (95 % CI)	<i>P</i> value
Previous adherence equal to 100 %*	+58 % (+45 %;+68 %)	<0.001
Education 8–10 years†	+7 % (–4 %;+14 %)	0.18
Education >10 years†	–12 % (–23 %;–1 %)	0.04
Physical activity in leisure time intermediate‡	+22 % (+9 %;+30 %)	<0.001
Physical activity in leisure time high‡	+26 % (+14 %;+30 %)	<0.001
Comorbidity§	+14 % (+6 %;+23 %)	0.002
LAMA		
Previous adherence equal to 100 %*	+39 % (+25 %;+53 %)	<0.001
LABA		
Previous adherence equal to 100 %*	+43 % (+26 %;+60 %)	<0.001
FEV ₁ (per 10 % increase in predicted value)	–8 % (–15 %;–1 %)	0.03
Males	+19 % (+6 %;+33 %)	0.007

COPD chronic obstructive pulmonary disease, *FEV₁* forced expiratory volume in one second

The ± values for adherence represent percent increase (+) or decrease (–) in adherence

*Previous adherence equal to 100 % in the year before the examination

†Reference group: less than eight years of education. ‡Reference group: physical activity in leisure time low

§See Table 1 and Appendix-Table 2 (available online) for the definition of comorbidity

examination. However, users of maintenance medications could switch or add therapy due to side effects or advice from their physicians. Therefore, in a sensitivity analysis, we studied adherence among the 72 % of our users who used only one type of maintenance medication in a one-year period. In this analysis, we observed very similar levels of adherence as reported in our main analysis, and we therefore believe that the 28 % of our users who potentially either switched or added therapy also have very similar levels of adherence. Furthermore, the time period from the examination until receiving the first dispensed prescription could affect our estimates of adherence. Therefore, in an additional sensitivity analysis, we calculated adherence in a one-year period from the user's first dispensed prescription, including the first dispensed dosage, and we also observed similar levels of adherence in this analysis.

The results of our multivariable analyses are in concordance with the findings of a recent cohort study by Huetsch et al.,²⁵ confirming previous adherence as the dominant predictor of future adherence. Interestingly, however, when previous adherence was not included as a possible variable in our multivariable sensitivity analysis, a high FEV₁ was consistently and significantly associated with decreased adherence. This could indicate that including previous adherence in multivariable modelling may introduce some degree of collinear masking of other important variables. To our knowledge, our study is the first to show an association between the level of physical activity in leisure time and the level of adherence to maintenance medication. This

association could represent general adherence to advice and recommendations. Interestingly, higher education was associated with decreased adherence to maintenance medication. This observation supports findings from a survey on self-reported inhaler use in COPD.²⁶ A possible explanation could be that highly educated individuals may choose to rely more on their own judgment and may adjust dosages to perceived symptoms rather than simply follow a fixed-dosage regime. It has been reported that comorbidity was associated with reduced odds of treatment with medication in COPD.⁴ In this study, comorbidity was associated with higher adherence, possibly explained by a perceived increase in symptoms in patients with both COPD and comorbidity,²⁷ resulting in increased adherence.

The recognized underdiagnosis of COPD in the general population²⁸ is a possible bias in our results. However, every participant with COPD in the Copenhagen General Population Study was informed of the results of their pulmonary function tests and was encouraged to consult their general practitioner. In addition, the participants were sent a letter with the results of the pulmonary function tests to be taken to their general practitioners. Therefore, we believe that a possible bias related to underdiagnosis was mitigated, since all analyses were applied to time intervals after the examination.

Inpatient administration of medications could have affected our estimates. However, the amount of maintenance medications sold to hospitals during the study period was approximately 1–2 % of the total amount sold.²⁹ Therefore, we believe that inpatient maintenance medication administration during hospitalizations could only slightly affect our estimates of medication use. In addition, it has been shown that out-of-pocket costs for medication may affect non-adherence,³⁰ and that non-adherence caused by out-of-pocket costs is particularly low in Scandinavia,³⁰ likely as a result of governmental reimbursement for medication.³¹ Reimbursement is the same in Denmark for all medications in our study. Therefore, our low estimates of adherence might be even lower in other populations.

In some of the previous studies indicating low adherence in COPD, the distinction between COPD and asthma was difficult due to lack of pulmonary function tests or medical history.^{5,6} A strength of our study is that we had information on both presence of asthma and lung function. On the other hand, the study was limited by the fact that we had only pre-bronchodilator pulmonary function test values. Therefore, we may have inadvertently included some individuals with asthma.

Since this study is pharmacoepidemiological, it shares the same limitation as all other pharmacoepidemiological studies in that we cannot be sure whether the individual who physically retrieves a dispensed prescription at the pharmacy actually adheres correctly to use of the medication. There are several possible important factors that could affect adherence, such as the patient's willingness/reluctance towards using medication, a poor inhaler technique, and stockpiling of medication. Therefore, real-life adherence to maintenance medication in COPD could be considerably lower than the upper limit of available dosages we report in this study.

As another limitation, the GOLD 1–4 grading that has been used throughout the last decade recommends long-acting bronchodilators only in GOLD grades 2–4.¹⁰ Use of maintenance medications in the GOLD 1 group in our study was very low. Nevertheless, approximately 16 % of our users of ICS/LABA had mild COPD. This observation seems to support a recent study indicating a tendency toward overtreatment with inhaled corticosteroids in mild COPD.³²

Lastly, as a minor limitation, the GOLD A–D grading was not officially implemented in clinical practice until 2011.¹⁰ Nevertheless, our analyses clearly show that the GOLD A–D grading was already an important driver of treatment in COPD in the general population even before the official implementation.

In conclusion, use of and adherence to maintenance medication in COPD in the general population was associated with severity of COPD as defined by GOLD, but even in severe and very severe COPD, use and adherence was low.

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Conflict of Interest: J.V. has received honoraria from GlaxoSmithKline, Almirall, AstraZeneca, Boehringer Ingelheim, Novartis, and Takeda for consulting and for presenting at meetings and symposia. P.L. has received honoraria from GlaxoSmithKline and other pharmaceutical companies for consulting and teaching and for presenting at meetings and symposia. J.H. has participated in research projects funded by Novartis, Pfizer, MSD, Nycomed, and ALK-Abelló, with grants paid to the institution where he was employed, and has received fees for teaching or consulting from Nycomed, Pfizer, Novartis, AstraZeneca, and other pharmaceutical companies. T.S.I., J.L.M., M.D., and B.G.N. have nothing to declare.

Author Contributions: J.V., B.G.N., and P.L. obtained the funding. J.V., P.L., and T.S.I. wrote the protocol. M.D. and B.G.N. collected the data. J.L.M. and T.S.I. performed the statistical analysis. T.S.I., J.L.M., P.L., J.H., and J.V. analyzed and interpreted the data. T.S.I. wrote the manuscript. J.V., J.L.M., P.L., M.D., J.H., and B.G.N. revised the manuscript. T.S.I. and J.L.M. had full access to all of the data in the study and take responsibility for the integrity and accuracy of the data analysis and for the submission.

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