

Quinine Use and the Risk of Exacerbations of Chronic Obstructive Pulmonary Disease: A Nationwide Retrospective Registry Study

Frida Vilstrup¹, Pradeesh Sivapalan^{1,2}, Josefin Eklöf¹, Alexander Jordan¹, Tor Biering-Sørensen^{3,4}, Søren Sperling⁵, Jens-Ulrik Stæhr Jensen^{1,2}

¹Department of Medicine, Section of Respiratory Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, 2900, Denmark;

²Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, 2200, Denmark; ³Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ⁴Department of Cardiology, Copenhagen University Hospital Herlev and Gentofte Hospital, Hellerup, Denmark; ⁵Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Denmark; Department of Clinical Medicine, Aarhus, 8000, Denmark

Correspondence: Frida Vilstrup, Gentofte Hospitalsvej 1D, Hellerup, 2900, Denmark, Tel +45 41180072, Email Frida.vilstrup@regionh.dk

Objective: Patients with chronic obstructive pulmonary disease (COPD) are a heavily comorbid group. Quinine is often used in the treatment of restless leg syndrome (RLS), although the adverse effects of the drug may be harmful for specific patient groups. The aim of this study was to determine the association between treatment with Quinine and the risk of acute exacerbations and mortality in patients with COPD, which has not previously been investigated.

Methods: Analyses were performed on data from Danish national registries containing information about the relevant patients and their health, prescriptions, hospital admissions, and outpatient clinic visits. A propensity score matched cohort was created by matching the population on known predictors of the outcome, and an unadjusted Cox proportional hazards regression analysis was performed. Lastly, a multivariable Cox analysis was performed on the entire, unmatched population, adjusting for the same variables as used in the propensity matching.

Results: The study population consisted of a cohort of 56,691 eligible patients with COPD, of whom 3,139 were exposed to Quinine. The propensity score matching led to two groups of 2,537 COPD patients, where one group was exposed to Quinine (cases) and the other group was not (controls). Exposure to Quinine was associated with an increased risk of exacerbations or death in a sensitivity analysis of the propensity-score-matched population (Hazard Ratio (HR) 1.130, 95% Confidence Interval (CI) 1.03 to 1.24). An unadjusted analysis on the unmatched population showed similar results (HR 1.475, 95% CI 1.39 to 1.56).

Conclusion: In the current study, we found an association between the use of Quinine in patients with COPD and an increased risk of acute exacerbations and death. The results must be interpreted with attention to the observational nature of the study, and in order to definitively determine the association, further investigations should be performed.

Keywords: COPD, pulmonary medicine, pharmacological interventions, COPD exacerbations

Background

Chronic Obstructive Pulmonary Disease (COPD) is one of the main causes of chronic morbidity and mortality worldwide.¹ A key feature of the disease is airway obstruction due to inflammation, breakdown of the lung parenchyma, and loss of elastic recoil.^{2,3} Acute exacerbations of COPD (AECOPD) are a significant driver of both hospital admissions and death among this patient group. Age is a risk factor for COPD and symptoms often worsen over time.⁴

Idiopathic muscle cramps are a common and distressing phenomenon, that often occurs in the legs as the so-called restless leg syndrome (RLS). Similar to COPD, RLS prevalence and severity increase with age⁵ with a substantial proportion of COPD patients suffering from RLS.^{5–8} One observational study from 2011 showed that more than 50% of patients with COPD suffered from RLS symptoms, whereas only 5.9% of the healthy control group suffered from the

symptoms.⁹ This is a heavily comorbid patient group, for whom especially cardiovascular diseases play a large and important role, alongside the pulmonary consequences of the disease.¹ Quinine is commonly used in treatment of RLS.¹⁰

The exact mechanism, by which Quinine works, has not been established, but it is known that it decreases the excitability of the motor end plate. This leads to a reduced response to nerve stimulation and increases the muscle refractory period and thereby reduces its response to repetitive stimulation.¹¹ These physiological mechanisms are related to the blockage of sodium and potassium channels, which are also related to the release of neurotransmitter from airway nerves.

It is not clarified whether Quinine also affects elements of COPD such as bronchoconstriction, production of mucus, and airway inflammation.^{12,13} Fatal adverse effects of Quinine use in persons with pulmonary diseases have been reported,^{14–18} however, a specific correlation has not previously been systematically investigated.

In the original use of Quinine in malaria treatment, the dosage is usually 600 mg three times a day, while the dosage for treatment of muscle cramps is usually 200–300 mg once daily. This minimizes the dose-related adverse effects of the drug though the drug may carry some side effects even at lower doses.¹⁰

In 2006, the US Food and Drug Administration warned against the use of Quinine to treat muscle cramps because of efficacy and safety issues.¹⁹ In 2018, the Danish Medicines Agency changed the status on drugs containing minimum 100 mg Quinine from over the counter to by prescription.²⁰ This change was based on the European Medicines Agency's recommendations, which state that Quinine entails an increased mortality risk in patients with heart failure.²¹

We hypothesized that the use of Quinine is associated with an increased risk of AECOPD and death. The aim of the study was to clarify whether this connection may be present.

Materials and Methods

Study Design

This study was a national observational cohort study based on data from Danish registries. The period of inclusion was from 1 January 2010 to 31 December 2018, and patients were followed 1 year after inclusion. Study entry was defined as the first outpatient clinic visit registered in Danish Registry of COPD (DrCOPD).

The primary outcome was severe exacerbations of COPD within 12 months after study entry or death in the same period. Death was included as a component in the primary outcome as it is a prominent competing risk in patients with COPD. The secondary outcome was moderate exacerbations of COPD.

Severe exacerbations were defined as exacerbations leading to hospital admission, whereas moderate exacerbations were defined as leading to the patient receiving a prescription of prednisolone and/or respiratory antibiotics, following the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification.¹ Respiratory antibiotics included amoxicillin, amoxicillin with clavulanic acid, benzylpenicillin, phenoxymethylpenicillin, moxifloxacin, azithromycin, roxithromycin, clarithromycin, doxycycline and ciprofloxacin. All Anatomical Therapeutic Chemical (ATC) classification codes are presented in online [Supplemental appendix 1](#).

Reporting adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.²² A study protocol was web published prior to conducting the study.²³

Data Sources

Three registries were used in the study. Each Danish citizen is given a personal identification number at birth, allowing linkage between registries.

The DrCOPD²⁴ is a Danish nationwide database, which contains information on health status and treatment of patients diagnosed with COPD. From DrCOPD, we obtained data regarding inclusion date, forced expiratory volume in 1 s (FEV1), Medical Research Council (MRC) dyspnea scale, body mass index (BMI), smoking history, age, sex, and date of death.

The Danish National Health Service Prescription Registry (NPR)²⁵ is administered by the Danish Health and Medicines Authority and it contains information on all prescriptions dispensed in Denmark. From this register, we used data on date of dispensations and dose and strength of prescriptions.

The Danish National Patient Register (DNPR)²⁶ is also administered by the Danish Health and Medicines Authority. The database contains information on both hospital admission and outpatient clinic visits, with diagnoses registered with the International Classification of Disease 10th revision (ICD-10 codes).

Study Population

The participant population for this study includes all patients diagnosed with COPD with an outpatient clinic visit registered in DrCOPD from year 2010 to 2018.

Patients with a malignant cancer diagnosis within 5 years before study entry (except non-melanoma cancer of the skin) were excluded from the study. These diagnoses are presented by ICD-10 codes in online [Supplemental appendix 2](#). Furthermore, patients younger than 40 years were excluded.

Patient and Public Involvement

No patients were involved in the design or conduct of this study.

Permission for our use of registry data was given by the Danish Data Protection Agency. Such retrospective use of data does not require ethical permission or patient consent in Denmark.

Statistical Analyses

Baseline characteristics were presented as frequencies and proportions for the matched and unmatched populations. A $p < 0.05$ was considered statistically significant.

A propensity score-matched cohort was created by matching the entire, eligible population on GOLD stage (1–4), age group (1–4), sex (male/female), BMI group (1–5), smoking history (group I: active smoker/group II: previous smoker or never smoker), number of AECOPD 12 months prior to baseline (0, 1, >2), inclusion year, Charlson Comorbidity Index 10 years prior to inclusion date (group I: 0–2 points = mildly ill, group II: 3–4 points = moderately ill, group III: >5 points: severely ill),^{27,28} prescription of long-acting β_2 -agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS) 1 year before inclusion in the study. We then used an unadjusted Cox proportional hazards regression model to assess the outcome of the propensity score-matched population. Lastly, a multivariable Cox proportional hazards model was performed on the entire, unmatched population, which was adjusted for the same variables as matched for in the previously described analyses.

Model control of the assumptions for the Cox proportional hazards model was performed and continuous variables that did not demonstrate linearity were categorized accordingly. No interaction between time and exposure was found, confirming the assumption of hazard proportionality.

There was only missing data in GOLD stage (FEV1), BMI group, and smoking status. The missing values were found in the next outpatient visit and in cases where this was not possible multiple imputation of the relevant variables was performed.

Data management and statistical analyses were performed using Statistical Analysis Software V.9.4 (SAS Institute). Propensity score matching was performed in the SAS PSMATCH-procedure based on the logit of propensity score, with a caliper of 0.25 and using an extended common support region. In all survival analyses, ties were handled with the Efron method.

Results

Study Participants

We identified 116,671 patients registered in DrCOPD, of whom 56,691 met all criteria for inclusion in the study. Of these patients, 3,139 were treated with Quinine, as seen in [Figure 1](#).

Baseline characteristics of the individuals in the unmatched and the matched population are presented in [Table 1](#) for both the exposed and the non-exposed group. The unmatched population consisted of 27,778 females (51.9%) and 25,774 males (48.1%) in the control group and 2,025 females (64.5%) and 1,114 males (35.5%) in the group exposed to Quinine.

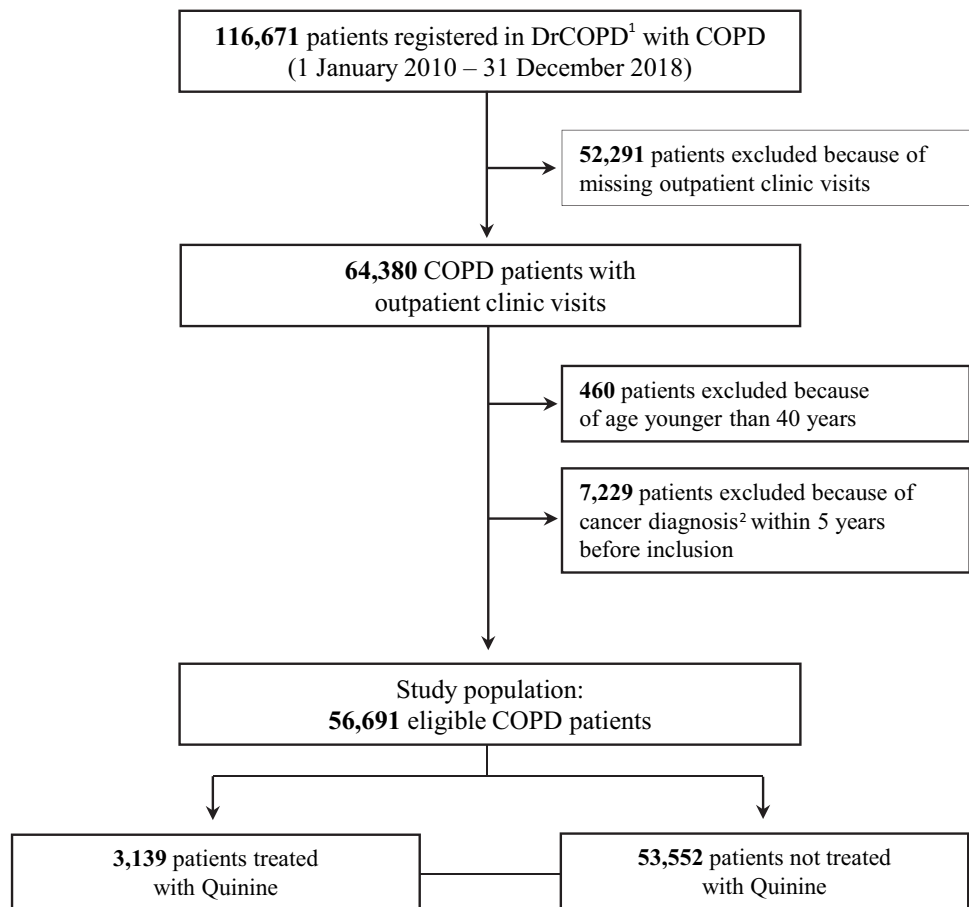


Figure 1 Study flowchart.
Notes: 1. Danish registry of Chronic Obstructive Pulmonary Disease 2. Malignant cancer diagnosis except non-melanoma cancer of the skin, ICD-10 codes presented in [Appendix 2](#).

In general, persons in the Quinine group were older, more likely to be female, less likely to smoke, and had more comorbidities than the control group. Other than that, the two groups were comparable.

The propensity score matching resulted in two groups of 2,537 persons, of whom one group was exposed to Quinine and one was not. Baseline characteristics of the population were obviously similar in the exposed and the non-exposed group. Furthermore, the Quinine user group in the matched population is comparable to the Quinine user group in the unmatched population on all variables.

Table 1 Baseline Characteristics

	Matched Population ¹		Entire, Unmatched Population	
	Quinine Users	Non-Users	Quinine Users	Non-Users
Variables n (%)	n = 2,537	n = 2,537	n = 3,139	n = 53,552
GOLD Stage ²				
GOLD 1	159 (6.3)	136 (5.4)	181 (5.8)	3,423 (6.4)
GOLD 2	1,077 (42.5)	1,038 (40.9)	1,218 (38.8)	20,780 (38.8)
GOLD 3	960 (37.8)	981 (38.7)	1,076 (34.3)	17,587 (32.8)
GOLD 4	341 (13.4)	381 (15.1)	384 (12.2)	6,813 (12.7)
Missing data	0 (0)	0 (0)	280 (8.9)	4,949 (9.2)

(Continued)

Table 1 (Continued).

	Matched Population ¹		Entire, Unmatched Population	
	Quinine Users	Non-Users	Quinine Users	Non-Users
Age Group				
<60 years	237 (9.3)	219 (8.6)	287 (9.1)	10,874 (20.3)
60–68 years	468 (18.4)	510 (20.1)	587 (18.7)	12,578 (23.5)
68–76 years	794 (31.3)	782 (30.8)	952 (30.3)	14,774 (27.6)
>76 years	1,038 (40.9)	1,026 (40.4)	1,313 (41.8)	15,326 (28.6)
Age, median (IQR)	73.7 (76.0–80.0)	73.9 (66.7–80.3)	74.1 (67.1–80.2)	69.8 (62.0–77.1)
Sex				
Female	1,620 (63.9)	1,607 (63.3)	2,025 (64.5)	27,778 (51.9)
Male	917 (36.1)	930 (36.7)	1,114 (35.5)	25,774 (48.1)
BMI Group ³				
<18.5	214 (8.4)	230 (9.1)	245 (7.8)	4,645 (8.7)
18.5–25	903 (35.6)	940 (37.1)	1,029 (32.8)	18,801 (35.1)
25–30	787 (31.0)	734 (28.9)	898 (28.6)	14,525 (27.1)
30–35	391 (15.4)	411 (16.2)	434 (13.8)	7,084 (13.2)
>35	242 (9.5)	222 (8.8)	264 (8.4)	3,786 (7.1)
Missing data	0 (0)	0 (0)	269 (8.6)	2,407 (8.6)
BMI, median (IQR)	25.0 (22.0–29.8)	25.0 (21.8–29.9)	25.0 (22.0–29.3)	25.0 (21.2–29.0)
Smoking Status				
Never smoker	67 (2.6)	70 (2.8)	67 (2.1)	1,569 (2.9)
Previous/passive smoker	1,641 (64.7)	1,649 (65.0)	1,691 (53.9)	26,533 (49.5)
Current smoker	829 (32.7)	818 (32.2)	849 (27.0)	16,433 (30.7)
Missing data	0 (0)	0 (0)	532 (16.9)	9,017 (16.8)
No. severe exacerbations 12 months prior				
0	1,316 (51.9)	1,326 (52.3)	1,622 (51.7)	31,919 (59.6)
1	228 (9.0)	222 (8.8)	284 (9.0)	4,251 (7.9)
>2	993 (39.1)	989 (39.0)	1,233 (39.3)	17,382 (32.5)
No. moderate exacerbations 12 months prior				
0	471 (18.6)	458 (18.1)	600 (19.1)	14,778 (27.6)
1	413 (16.3)	410 (16.2)	514 (16.4)	9,799 (18.3)
>2	1,653 (65.2)	1,669 (65.8)	2,025 (64.5)	28,975 (54.1)
Charlson Comorbidity Index Group ⁴				
Group I	235 (9.3)	212 (8.4)	280 (8.9)	7,705 (27.4)
Group II	784 (30.9)	802 (31.6)	21,337 (39.8)	13,065 (46.5)
Group III	1,518 (59.8)	1,523 (60.0)	22,065 (41.2)	7,350 (26.1)
Prescription ⁵ 12 months prior (yes)				
Long-acting β_2 -agonists	2,196 (86.6)	2,086 (82.2)	2,654 (84.5)	41,120 (76.8)
Long-acting muscarinic antagonists	2,069 (81.6)	1,979 (78.0)	2,452 (78.1)	37,745 (70.5)
Inhaled corticosteroids	2,042 (80.5)	1,845 (72.7)	2,466 (78.6)	37,089 (69.3)
Oral corticosteroids	1,284 (50.6)	1,267 (49.9)	1,553 (49.5)	22,225 (41.5)

Notes: 1. Propensity score matched on variables described in methods section 2. Severity of chronic obstructive pulmonary disease based on obstruction stage, GOLD 1: FEV1 >80% = mild, GOLD 2: 50% < FEV1 < 80% = moderate, GOLD 3: 30% < FEV1 < 50% = severe, GOLD 4, FEV1 < 30% = very severe, 3. Body mass index 4. Group I: 0–2 points = mildly ill, group II: 3–4 points = moderately ill, group III: > 5 points: severely ill,²⁸ 5. At least one prescription.

In total, 5,074 patients were matched on the variables described previously, 2,537 from, respectively, the Quinine group and the control group. The matched population consisted of 1,607 females (63.3%) and 930 (36.7%) males in the control group and 1,620 females (63.9%) and 917 males (36.1%) in the Quinine group.

Analyses

An unadjusted Cox proportional hazard model was performed on the propensity score matched population at 12-months follow-up, in which treatment with Quinine showed an increase in the risk of AECOPD and death (Hazard Ratio (HR) 1.13, 95% Confidence Interval (CI) 1.03 to 1.24).

Similar results were found in an unadjusted Cox model on the unmatched population (HR 1.475, 95% CI 1.39 to 1.56). Furthermore, an adjusted Cox proportional hazard model performed on the unmatched population showed the same tendency (HR 1.23, 95% CI 1.15 to 1.31). The HRs for these analyses and all variables in the adjusted analysis are presented in Figure 2.

In the propensity score matched population, 1,001 persons exposed to Quinine had an event (AECOPD or death) within 12 months follow-up, whereas 906 persons in the group not exposed to Quinine had a similar event in the same period. This translates to 39.49% in the exposed group and 35.71% in the non-exposed group. In the unadjusted population, the signal was similar, as 39.41% (n = 1,237) in the Quinine group had an event and 28.77% (n = 15,409) in the non-exposed group had one. The correlation in percentage is illustrated in Figure 3.

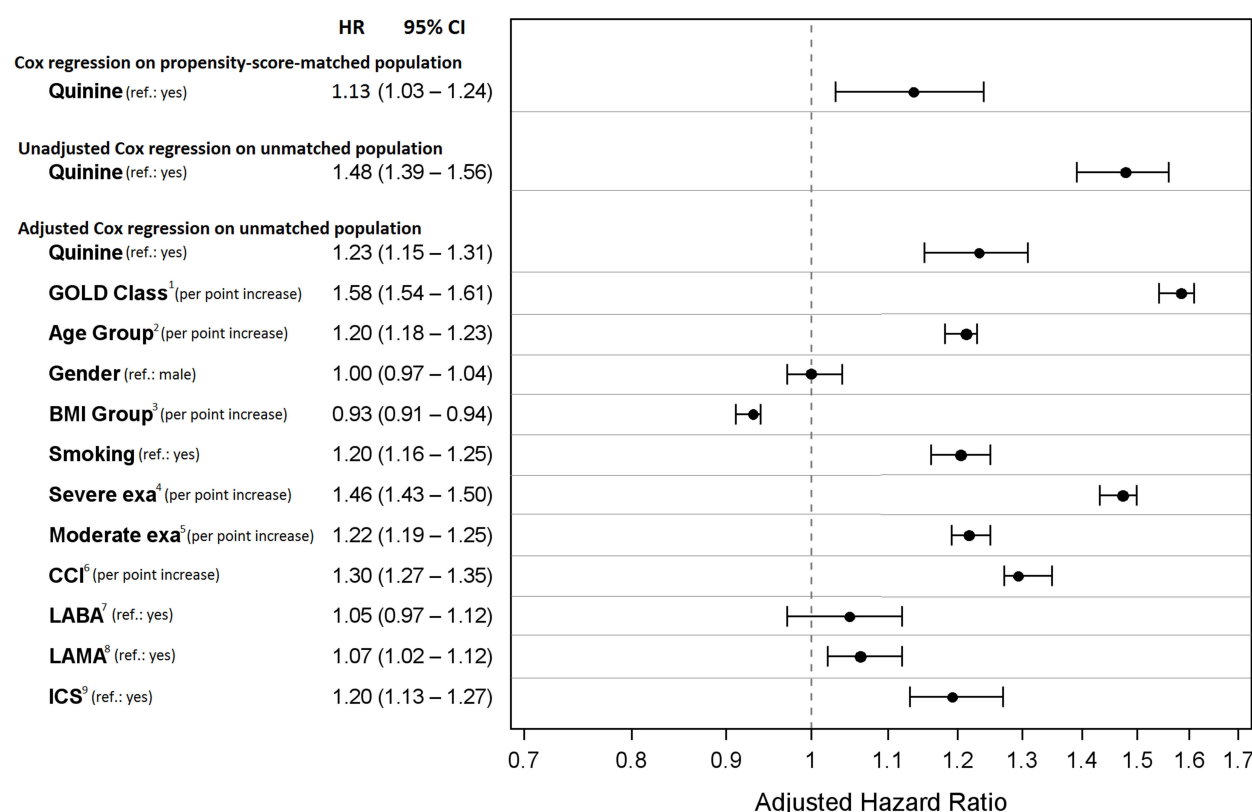


Figure 2 Forest plot of Hazard Ratios (HR) and 95% Confidence Intervals (CI).

Notes: 1. Severity of chronic obstructive pulmonary disease based on obstruction stage, GOLD 1: FEV1 > 80% = mild, GOLD 2: 50% < FEV1 < 80% = moderate, GOLD 3: 30% < FEV1 < 50% = severe, GOLD 4, FEV1 < 30% = very severe, 2. Age group 1: age < 60 years, group 2: 60 years < age < 68 years, group 3: 68 years < age < 76 years, group 4: 76 < age, 3. Body mass index, group 1: BMI < 18.5, group 2: 18.5 < BMI < 25, group 3: 25 < BMI < 30, group 4: 30 BMI < 35, group 5: 35 > BMI, 4. Severe exacerbation of COPD, within the last 12 months, defined as leading to hospital admission, group 1: 0, group 2: 1, group 3: >2, 5. Moderate exacerbation of COPD, within the last 12 months, defined as leading to the patient receiving a prescription of prednisolone and/or respiratory antibiotics, group 1: 0, group 2: 1, group 3: >2, 6. Charlson comorbidity index, group (I) 0–2 points = mildly ill, group II: 3–4 points = moderately ill, group III: >5 points: severely ill, 7. Long-acting β_2 -agonists, 8. Long-acting muscarinic antagonists, 9. Inhaled corticosteroids.

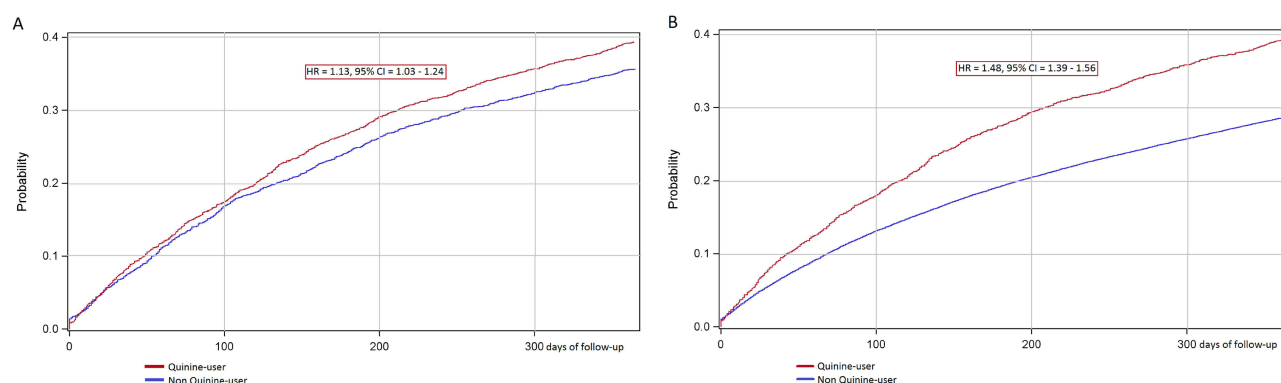


Figure 3 Cumulative Incidence Figure of events (AECOPD or death) in Quinine-users and non-users in **(A)** the Propensity Score Matched population and **(B)** the unadjusted population.

Notes: The Y-axis is a presentation of the probability of an event (AECOPD and/or death) and the X-axis represents days of follow-up after inclusion in the study. In the red box is presented the hazard ratio of events in sub-figure **(A)** the Propensity Score Matched Population and **(B)** the unadjusted population.

Discussion

In this nationwide registry-based cohort study, we found that the use of Quinine was associated with an increased risk of AECOPD. This association was significant both in analyses of the unmatched population and in analyses of the population matched on relevant variables.

The specific correlation between the use of Quinine and AECOPD has not previously been systematically investigated, though similar results have been proved with different patient groups.

A cohort study with a study population of 175,195 patients by Fardet et al from 2017 found a significantly increased mortality in persons exposed to Quinine compared to persons not exposed to the drug (HR 1.24, 95% CI 1.21–1.27).²⁹ Similar results were found in an observational study with a population of 135,529 patients by Gjesing et al from 2015. In this study, a slightly increased mortality risk with the use of Quinine alone was found (incidence rate ratio (IRR) 1.04, 95% CI 1.01–1.07).

The first-mentioned study included all patients with a prescription of Quinine for a minimum of 12 months. Meanwhile, the study by Gjesing et al focused only on patients with heart failure, as they often experience leg cramps and are commonly treated with Quinine.³⁰

The present study is the first large observational nationwide registry study that investigates the impact of treatment with Quinine on severe and moderate exacerbations of COPD in a real-life outpatient cohort with 12 months follow-up. The study had a large population size with more than 50,000 patients meeting all inclusion criteria. All patients were registered in national Danish registries, which allowed us to control for important confounders and thereby reduce the risk of bias and ensure no loss to follow-up. We thus have complete follow-up on all outcomes. DrCOPD enabled us to ensure a correct COPD diagnosis, made by a respiratory specialist and verified through spirometry during annual outpatient visits, thereby reducing the risk of misclassification bias. To reduce the risk of unmeasured “new user” bias, we propensity-score matched on several known predictors of the outcome and the survival analysis was adjusted for the same variables.

There are, however, also limitations to the current study. First, despite having adjusted the analyses for known confounders, the survival analysis suggested an increased risk of AECOPD with the use of LABA, LAMA and ICS, which indicates some residual bias by indication, since at least LAMA and ICS are documented to reduce AECOPD.^{31–33} Second, it was not possible, given the registry design, to monitor the patients’ adherence, as exposure to the drug in this study was defined by a collected prescription, which is what the databases provide information on. It was not possible to determine whether patients used the medication, which is an inborn error in the design of the retrospective registry study. However, the uncertainty is limited because we know the prescriptions are collected, which makes it very likely that the drugs were also used by the patients. Non-adherence would lead to a conservative bias since actual non-users would be classified as users. Third, the baseline data on the unmatched population showed significant differences between the two

groups especially in age, sex, and comorbidities described by the Charlson Comorbidity Index score. The difference in age and sex is bound to the patient group, as RLS occurs more often in women than in men and the occurrence increases with age. The difference in comorbidity does though entail some bias to the results, as the increased occurrence of AECOPD and death in the case-group could be related to the existing comorbidities rather than exposure to Quinine. However, the difference in number of exacerbations (both moderate and severe) between the two groups is not as large, which indicates that the found association is in fact linked to Quinine. This indication is accentuated by the results in the propensity score matched population. Here, difference in comorbidities was taken into consideration, and the results are similar to those in the unmatched population. Fourth, it was not necessary to have a prescription to buy Quinine in Denmark until year 2018, and therefore we must expect that there are more users of the drug than included in our study. It was though always financially more beneficial for patients to buy the drug with a prescription, and it becomes apparent in our data that a large number of patients did have prescriptions of Quinine in these years.

In conclusion, our analyses consistently suggest an association between treatment with Quinine and an increased risk of acute exacerbations and death in patients with COPD. Our data thus support the risk correlated with the use of this drug by people with COPD. Based on existing data on the effect of Quinine in other patient groups combined with knowledge on the mechanisms of COPD it makes theoretical sense that such an association would be evident. The result of this study emphasizes this association. The current recommendations against the use of Quinine in the treatment of RLS in Denmark are primarily targeted patients with heart failure, but the findings in this study indicate that these recommendations could also be relevant for patients with COPD. Moreover, the benefit should be weighed against the risks and thus nonpharmacologic interventions and other drugs, such as antiepileptics, calcium channel blockers, various vitamins and minerals have been investigated as possible substitutes for the treatment.

However, the results should be interpreted with reservation, as this was an observational study. To clarify the degree of residual confounding and determine whether Quinine is in fact the cause of the found risk, randomized controlled trials (RCT) should be performed. Our hypothesis is thus not definitively answered, but it seems very likely that there may exist an increased risk of exacerbations among COPD patients using Quinine.

Funding

This study was funded by the Novo Nordisk Foundation (No. NNF20OC0060657). The sponsor had no involvement in any of the stages from study design to submission of this paper.

Disclosure

Professor Tor Biering-Sørensen reports grants from Novo Nordisk, grants from GSK, grants from Boston Scientific, grants from Sanofi Pasteur, grants from Novartis, grants from Pfizer, grants from AstraZeneca, grants from GE Healthcare, personal fees from Novo Nordisk, personal fees from IQVIA, personal fees from Parexel, personal fees from Amgen, personal fees from CSL Seqirus, personal fees from GSK, personal fees from Sanofi Pasteur, personal fees from AstraZeneca, personal fees from Bayer, personal fees from Novartis, personal fees from GE healthcare, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Global Initiative for Chronic Obstructive Lung Disease, I.G. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2024 REPORT)*. 2023;218
2. Abboud RT, Vimalanathan S. Pathogenesis of COPD. part I. role of pro-tease-antiprotease imbalance in emphysema. *Mak J C W Pathogenesis COPD Part II*. 2008;12(4):361.
3. Vilstrup F, Heerfordt CK, Kamstrup P, et al. Renin-angiotensin-system inhibitors and the risk of exacerbations in chronic obstructive pulmonary disease: a nationwide registry study. *BMJ Open Respir Res*. 2023;10(1):e001428. doi:10.1136/bmjresp-2022-001428
4. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. *Thorax*. 2015;70(5):482–489. doi:10.1136/thoraxjnl-2014-206084
5. Lo Coco D, Mattaliano A, Lo Coco A, et al. Increased frequency of restless legs syndrome in chronic obstructive pulmonary disease patients. *Sleep Med*. 2009;10(5):572–576. doi:10.1016/j.sleep.2008.04.014
6. Du D, Zhang G, Xu D, et al. Prevalence and clinical characteristics of sleep disorders in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Sleep Med*. 2023;112:282–290. doi:10.1016/j.sleep.2023.10.034

7. Mandal T, Aydın Ş, Kanmaz D, et al. To what extent and why are COPD and Willis-Ekbom disease associated? *Sleep Breath.* 2016;20(3):1021–1027. doi:10.1007/s11325-016-1359-3
8. Thi Truong BE, Sung F-C, Lin C-L, et al. A follow-up study on restless legs syndrome in chronic obstructive pulmonary disease population. *Sleep Med.* 2021;80:9–15. doi:10.1016/j.sleep.2021.01.016
9. Aras G, Kadakal F, Purisa S, et al. Are we aware of restless legs syndrome in COPD patients who are in an exacerbation period? Frequency and probable factors related to underlying mechanism. *COPD J Chronic Obstructive Pulm Dis.* 2011;8(6):437–443. doi:10.3109/15412555.2011.623737
10. El-Tawil S, Al Musa T, Valli H, et al. Quinine for muscle cramps. *Cochrane Database Syst Rev.* 2010;(12).
11. Goodman L. *The Pharmacological Basis of Therapeutics.* New York, NY: McGraw-Hill Education; 2015.
12. Pelaia G, Gallelli L, Vatrella A, et al. Potential role of potassium channel openers in the treatment of asthma and chronic obstructive pulmonary disease. *Life Sci.* 2002;70(9):977–990. doi:10.1016/S0024-3205(01)01487-4
13. Malerba M, Radaeli A, Mancuso S, et al. The potential therapeutic role of potassium channel modulators in asthma and chronic obstructive pulmonary disease. *J Biol Regul Homeost Agents.* 2010;24(2):123–130.
14. Samaranayake CB, Yap E. Fatal quinine-induced thrombocytopenia from pulmonary haemorrhage. *Internal Med J.* 2014;44(4):423–425. doi:10.1111/imj.12393
15. Everts RJ, Hayhurst MD, Nona BP. Acute pulmonary edema caused by quinine. *Pharmacotherapy.* 2004;24(9):1221–1224. doi:10.1592/phco.24.13.1221.38087
16. Krantz MJ, Dart RC, Mehler PS. Transient pulmonary infiltrates possibly induced by quinine sulfate. *Pharmacotherapy.* 2002;22(6):775–778. doi:10.1592/phco.22.9.775.34070
17. Rahman M, Hashmey R, Abuhasna S. Quinine-induced bronchiolitis obliterans and organizing pneumonia. *J Anaesthesiol Clin Pharmacol.* 2012;28(4):505–507. doi:10.4103/0970-9185.101942
18. Raine D, Lee A, Wiedmann R. Flash pulmonary oedema: a rare but serious side effect of quinine sulphate. *BMJ Case Rep.* 2012;2012.bcr0320114040.
19. Food and Drug Administration, D.o.H.a.H.S. Drug products containing quinine; enforcement action dates. *Fed Regist.* 2006;71(241):4.
20. Lægemiddelstyrelsen, D.M.A. Ændring af udleveringsgruppe for lægemidler, der indeholder kinin. 2078; Available from: <https://laegemiddelstyrelsen.dk/da/nyheder/2018/aendring-af-udleveringsgruppe-for-laegemidler-der-indeholder-kinin/>. Accessed May 12, 2025.
21. (PRAC), P.R.A.C. *PRAC Recommendations on Signals.* European Medicines Agency; 2016.
22. Cuschieri S. The STROBE guidelines. *Saudi J Anaesth.* 2019;13(5):S31–S34. doi:10.4103/sja.SJA_543_18
23. Vilstrup F. *Protocol: treatment with Quinine and the risk of exacerbations and mortality in patients with chronic obstructive pulmonary disease.* 2023; Available from: <https://coptrin.dk/wp-content/uploads/2023/10/Quinine-COPD-protocol.pdf>. Accessed May 12, 2025.
24. Lange P, Tøttenborg S, Sørensen A, et al. Danish register of chronic obstructive pulmonary disease. *Clin Epidemiol.* 2016;Volume 8:673–678. doi:10.2147/CLEP.S99489
25. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, et al. Data resource profile: the Danish national prescription registry. *Int J Epidemiol.* 2017;46(3):798. doi:10.1093/ije/dyw213
26. Schmidt M, Schmidt SAJ, Sandegaard JL, et al. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol.* 2015. 449–490. doi:10.2147/CLEP.S91125
27. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130–1139. doi:10.1097/01.mlr.0000182534.19832.83
28. Charlson.-1987.-Comorbidity (1).
29. Fardet L, Nazareth I, Petersen I. Association between long-term quinine exposure and all-cause mortality. *JAMA.* 2017;317(18):1907–1909. doi:10.1001/jama.2017.2332
30. Gjesing A, Gislason GH, Christensen SB, et al. Use of quinine and mortality-risk in patients with heart failure—a Danish nationwide observational study. *Pharmacoepidemiol Drug Saf.* 2015;24(3):310–318. doi:10.1002/pds.3746
31. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med.* 2018;378(18):1671–1680. doi:10.1056/NEJMoa1713901
32. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet.* 2018;391(10125):1076–1084. doi:10.1016/S0140-6736(18)30206-X
33. Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? *Int J COPD.* 2018; Volume 13:2587–2601. doi:10.2147/COPD.S172240

International Journal of Chronic Obstructive Pulmonary Disease

Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols. This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>

Dovepress
Taylor & Francis Group