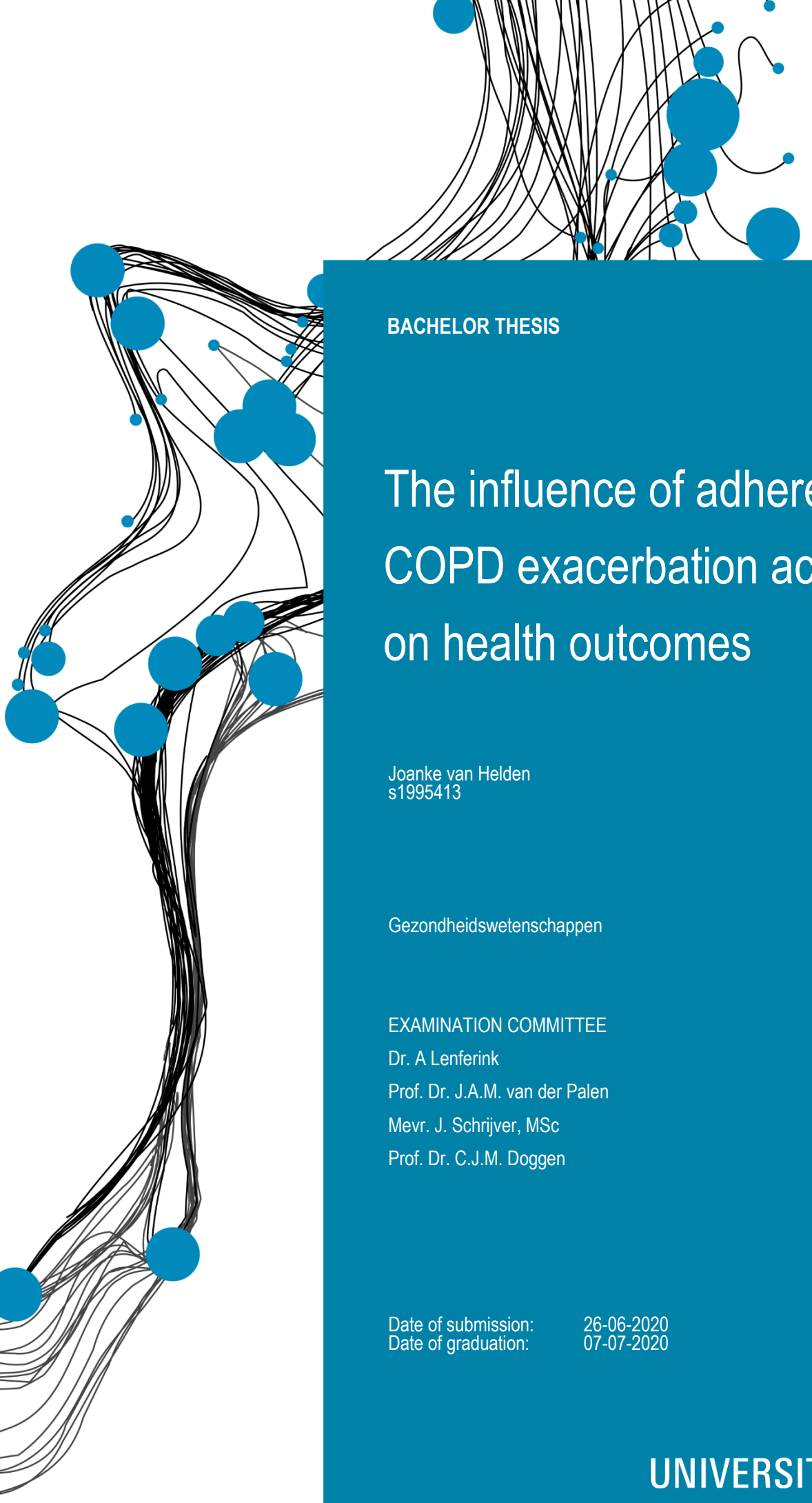

BACHELOR THESIS

The influence of adherence to COPD exacerbation action plans on health outcomes

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Gezondheidswetenschappen

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Contents

Abstract

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death worldwide. Exacerbations are a major part of its disease burden. COPD exacerbation action plans are effective methods for self-management, but adherence to these plans is low. Studies on the effect of adherence to COPD exacerbation action plans found adherence reducing the duration of COPD exacerbations, hospital visits, anxiety and depression. Most of these studies considered patients as being either adherent or not. The effect of timing of adherence to COPD exacerbation action plans on health outcomes is not known. The aim of this study was to determine the effect of timing of adherence to COPD exacerbation action plans in patients who experienced COPD exacerbations or took a course of oral prednisolone from the COPD exacerbation action plans groups in the COPE-II and COPE-III studies.

Methods: This study was a retrospective cohort study over a twelve-month period. Timing of adherence was categorized in four categories: “optimal treatment”, “suboptimal treatment”, “significant delay or no treatment” and “treatment outside actual exacerbation period”. Studied health outcomes were the number of COPD exacerbations and of COPD exacerbation days, the average duration of COPD exacerbation, mortality, hospital visits, anxiety, depression and Health Related Quality of Life (HRQoL).

Results: In total, 145 patients were included: “significant delay or no treatment” (n=46), “suboptimal treatment” (n=17), “optimal treatment” (n=38) and “treatment outside the actual exacerbation period” category (n=44). Being in the “optimal” or “suboptimal” treatment category reduced the number of COPD exacerbation days by 32.8-33.8 days ($p<0.05$) and the duration of COPD exacerbations by 7.4-6.6 days ($p<0.05$) compared to the “significant delay or no treatment” category. Patients in the “significant delay or no treatment” and “optimal treatment” categories significantly and clinically relevantly deteriorated on the Chronic Respiratory Questionnaire dyspnoea domain. No significant results were found in any other category.

Conclusion: Being adherent to a COPD exacerbation action plan by taking a course of oral prednisolone within two days prior to or after the start of a COPD exacerbation appears to contribute to shorter durations of COPD exacerbations and less COPD exacerbation days per year. Results on HRQoL are inconclusive. The timing of adherence to COPD-exacerbation action plans does not seem to influence hospitalizations and anxiety and depression.

Introduction and research question

Chronic obstructive pulmonary disease (COPD) is a chronic, treatable lung-disease and is one of the worldwide leading causes of death.[1] In 2016, COPD ranked at number three in the worldwide top ten causes of death.[2] COPD patients can develop exacerbations: episodes of acutely worsening respiratory problems and symptoms.[1] Patients with exacerbations can experience dyspnoea, or other symptoms like coughing and wheezing. These exacerbations form an important part of the disease burden that COPD poses both economically and medically.[1,3,4] For instance, because medication is necessary and severe exacerbations often require hospital admissions. [1] Patients with COPD often have comorbidities, such as cardiac disease, diabetes and anxiety and depression. In a 2015 study it was reported that 78.6% of COPD patients had at least one comorbidity and 47.9% of patients had been diagnosed with three or more comorbidities.[5] Comorbidities sometimes have a symptom overlap with COPD exacerbations.[6] Dyspnoea, for instance, can occur both in exacerbations of cardiac disease and COPD.

There have been many studies regarding self-management in COPD-patients, studying the (cost)effectiveness of COPD self-management interventions. The motivation behind this can be that self-management might be able to reduce the costs of COPD's disease burden and might help patients to cope with their disease.[7,8] A Delphi-study by Effing et al. [9] found the following definition of a COPD self-management intervention (shortened): *"structured but personalised and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease."*

A possible component of self-management in COPD is the use of exacerbation action plans. An action plan instructs a patient on the actions he or she could undertake when experiencing a COPD exacerbation.[10,11] For instance, starting medication when a COPD exacerbation occurs or talking to a medical professional. Much research has been done with regard to action plans focussed on self-treatment of COPD exacerbations. In a Cochrane systematic review on this subject by Lenferink et al. it was concluded that there is a positive association between the use of COPD exacerbation action plans and Health Related Quality of Life (HRQoL) and a negative association between the use of action plans and hospital admissions.[10] This means that patients who used action plans experienced better quality of life and had to be admitted to hospital less often than patients who did not use action plans. In a randomized controlled trial (RCT) performed by Effing et al., (the COPE-II study) the (cost)-effectiveness of a self-management intervention including COPD exacerbation action plans was studied in an RCT among 142 COPD-patients. In this study a significant reduction in number of exacerbation days was found in the self-treatment group among patients with more than 137 COPD exacerbation days per year in comparison to similar patients from the control group. Also, a significant reduction in the number of health-care visits was found in the intervention group when compared to the control group.[7] In a RCT by Lenferink et al., (the COPE-III study) the effects of COPD exacerbation action plans on multiple health outcomes were studied in 201 patients diagnosed with COPD and at least one comorbidity. Included comorbidities were: ischemic heart disease, heart failure, diabetes, anxiety and depression. Patients received action plans both for exacerbations in COPD and the comorbidities they were diagnosed with. In this study, a significant and clinically relevant reduction was found in the duration of COPD exacerbations between patients in the intervention group (median 8.1 days) and patients in the control group (median 9.5 days). In addition, the risk of hospital admissions related to respiratory issues was significantly lower in the intervention group.[12]

However, most of the studies regarding COPD exacerbation action plans do not study the effect of adherence, i.e. the extent to which a patient follows the instructions given by the action plans. In

some studies, it is reported that only 40% of patients actually adhere to their action plans. [11] This possibility of low adherence makes it difficult to determine to what extent following the action plans' instructions is required to obtain the benefits associated with the use of action plans.

Some research has been done with regards to the effect of adherence to COPD action plans on health outcomes. In a study by Bischoff et al. [3]the effect of adherence to COPD exacerbation action plans on the duration of exacerbations, ergo the recovery time, was studied. In the analysis, 217 exacerbations of 119 patients were included. Patients were considered adherent in 87 (40%) of these cases. In this study a significant reduction of recovery time (-5.1 days) was found in adherent patients. Remarkable in the study by Bischoff et al. [3] is that less than 50% of patients included in this study were reported to have comorbidities. The relatively low percentage of patients diagnosed with comorbidities in the study of Bischoff et al. [3] compared to the 78.6% described in the study mentioned earlier might lower the extent to which the result from that study can be generalized to the entire COPD population, as comorbidities have a high prevalence among COPD-patients.[5] Farias et al.[13] conducted a pilot study in which patients who had severe comorbidities and/or any diseases which might cause dyspnoea were excluded. The authors of this study saw a significant effect of adherence to exacerbation plans by starting with prednisolone within 72 hours of the start of a COPD exacerbation, on the recovery time after COPD exacerbations. In a study by Choi et al.[14], COPD-patients with comorbidities were included. However, duration of exacerbations was not studied in this research. Primary outcomes in this study were the number of hospital admissions, the level of anxiety and depression and knowledge on COPD. A higher level of adherence was associated with less unplanned hospital visits, anxiety and depression and was associated with higher levels of knowledge on COPD.

The studies mentioned above suggest that strict adherence to COPD exacerbation action plans might reduce the duration of exacerbations, the amount of hospital visits and the level of depression and anxiety experienced by COPD-patients. However, adherence can be defined in many ways. [15] Also, it consists of both the sort of action that was taken, and the timing of this action. The definitions of adherence varied across the aforementioned studies. Bischoff et al. [3] considered adherence a binary variable, stating that one was either adherent or not. Two analyses were performed, with different definitions of adherence. Adherence was defined as starting with antibiotics and prednisolone within either two or three days of the start of a COPD exacerbation, according to the action plan. While Farias et al.[13] did use different categories of adherence, these were only based on the action a patient took, i.e. taking medication or going to a hospital, and not its timing. Adherence to the instruction to take a course of oral prednisolone was only measured as either adherent within 72 hours or not adherent. Choi et al. [14] on the other hand determined the level of adherence on a 4-point Likert scale in a cross-sectional study. Patients used this scale to document looking back per action (e.g. taking antibiotics on time) whether they did this "never", "some of the time" "most of the time" or "all of the time", when their symptoms got significantly worse and thus the study focussed on the content of the actions that were taken. None of these studies compared multiple different categories of timing adherence against one another. This means that, based on literature, no conclusions can be made as to whether or not the timing of adherence to the COPD exacerbation action plan influences health outcomes. It might be that starting medication late or early is just as effective as being perfectly adherent all the time. Also, the overlap in symptoms between COPD and comorbid exacerbations mentioned earlier may limit the effectiveness of COPD specific exacerbation action plans in the population of COPD patients that do experience comorbidities. [12] After all, when symptoms of different diseases overlap a symptom-based COPD exacerbation action plan might be triggered when a different comorbidity is flaring up. [16]

The evidence discussed on the effects of adherence on health outcomes in COPD exacerbation action plans, comes from studies in which the population has a relatively low prevalence of comorbidities compared to the 78.6% found in another study.[3,5,13] Therefore, it is relevant to determine whether exacerbation action plan adherence is of significant influence on health outcomes in a more representative group (i.e. with a more similar percentage of comorbidities) of COPD patients as well. Previous studies would suggest a positive (i.e. reducing) influence on duration of exacerbations.[3,13] However, these studies do not take into account different levels in timing of adherence. Thus, they cannot be used to determine whether being adherent on the precise time the COPD exacerbation action plan instructs one to be, yields more benefits than following the action plan's instructions late or early. Other evidence would suggest a positive effect of adherence on anxiety and depression and hospital admissions. [14] Whether the timing of adherence to COPD exacerbation action plans influences health outcomes is not known. Therefore, the aim of this study is to investigate whether there is an association between the timing of adherence to COPD exacerbation action plans and health outcomes in patients who experienced COPD exacerbations while having been assigned to use COPD exacerbation action plans in the COPE-II and COPE-III studies.

Research question

What is the effect of different timing of adherence to COPD exacerbation action plans, by patients from the action plan group of two COPD self-management trials who experienced exacerbations and/or started an oral course of prednisolone, on various health outcomes?

Methods

Objective

This study's aim is to investigate whether the timing of adherence to COPD exacerbation action plans influences various health outcomes in COPD patients. Outcomes that were studied are the duration of COPD exacerbations and the number of unplanned hospital visits as well as HRQoL, mortality, anxiety and depression.

Design

This study is a retrospective cohort study, based on pooled data from self-treatment intervention groups from two RCTs that evaluated the effectiveness of COPD self-management interventions including COPD exacerbation action plans.

Population

The data used was extracted from the COPE-II and the COPE-III study.[7,12] While comorbidities were excluded in the COPE-II study, they were a criterion for inclusion in the COPE-III study. [7,12] In the COPE-II study, patients were selected from the region of Enschede, The Netherlands.[7] In the COPE-III study, patients were selected from hospitals in the Netherlands and Australia. [12] Eligible patients had already been filtered by inclusion and exclusion criteria from the studies from which data was obtained. Hence, these in- and exclusion criteria are summarized in the table 1 below:[7,16]

Table 1: Comparison of in and exclusion criteria from COPE-II and COPE-III study.[7,16]

	Both COPE-II and III	COPE-II specific	COPE-III specific
Criteria for inclusion	-Clinical COPD diagnosis according to GOLD [1] criteria. -Minimum of 3 exacerbations and/or 1 hospitalization due to respiratory problems in the 2 years prior to the study -Ability to read and understand Dutch/English -stable at time of inclusion -given written informed consent prior to inclusion -40 years or older - (history of) smoking	Forced Expiratory Volume (FEV) (1) * % predicted 25-80%	At least one of the following comorbidities: ischaemic heart disease, heart failure, Diabetes Mellitus, active symptoms of anxiety and/or depression
Criteria for exclusion	-Any other disease with low rate of survival -Other serious lung disease -enrolled in any other RCT	-Severe psychiatric illness - Uncontrolled Diabetes Mellitus (DM) during COPD exacerbation or hospitalization for DM in past two years. -Regular need for oxygen therapy -Any disorders or progressive diseases seriously influencing walking ability	a cognitive impairment, defined as a score lower than 24 on the Mini Mental State Examination [17]

For the current study, the following additional in- and exclusion criteria were used in selecting patients from the self-treatment intervention groups of the COPE-II and COPE-III studies. As COPD exacerbation action plans are triggered once an exacerbation starts, only patients who experienced exacerbations during their study's follow-up or patients who took action that would be required if they had an exacerbation will be included. In both COPE-II and COPE-III studies, missing data in the

symptom diaries were handled using a predefined algorithm.[12] Therefore, in this study, there are no 'missing' data on the duration of exacerbations anymore. Furthermore, if data on one of the studied health outcomes was missing at twelve months, that patient was excluded from analysis in that specific outcome.

Exposure

The exposure studied in this retrospective cohort study is the level of adherence to the COPD exacerbation action plans used in the COPE-II and COPE-III study.

Self-treatment intervention.

All patients received self-management training sessions including a COPD exacerbation action plan. [7,12] During these sessions patients were also given a card on which they described their 'usual' COPD symptoms. This card determined a baseline with which symptoms could be compared in order to determine whether these were 'usual', 'slightly increased' or 'significantly worse than usual'. All patients kept a diary in which they recorded their COPD symptoms. Patients were trained to use these diaries. If their symptoms were significantly worse than usual (as described on the 'what is usual for me'-card) for at least two days in a row, it was considered an exacerbation. The action plan then instructed a patient to start a course of oral prednisolone and when necessary a course of oral antibiotics as well. If this did not provide improvement in symptoms patients were instructed to contact the study office. [12]

The independent variable in this study is the level of adherence to the action plan, operationalized as the timing of taking action. Adherence in this study was defined as the extent to which patients initiated a course of oral prednisolone for the self-treatment of a COPD exacerbation according to the action plan, defined by the time between the start of a COPD exacerbation and the starting of a course of prednisolone by the patient.

In order to perform a comprehensive analysis, the timing of adherence was organised in four categories:[18]

1. Optimal treatment Adherence was defined optimal if a course of prednisolone was started at the start date of a COPD exacerbation, or one day either before or after the day a COPD exacerbation started.
2. Suboptimal treatment Adherence was defined suboptimal if a course of prednisolone was started two days either before or after the start date of a COPD exacerbation. Initiating no action during a COPD exacerbation that lasted between one and three days was also defined as suboptimal treatment.
3. Significant delay or no treatment. Initiating no action during a COPD exacerbation was defined as no treatment. Starting with a course of prednisolone three or more days after an exacerbation started but before it had ended was defined as significant delay.
4. Treatment outside the actual exacerbation period. When patients started a course of prednisolone three or more days before a COPD exacerbation started, or started with medication after a COPD exacerbation had ended, this was considered treatment outside of the actual period of an exacerbation.

The allocation of patients in categories of adherence was done by first determining the category of adherence per COPD exacerbation, for each COPD exacerbation during the twelve-month follow-up. Then for each patient the number of times they were in each category of adherence was counted. When patients acted differently in different exacerbations, for instance starting prednisolone late in some of the COPD exacerbations and on the start date in others, the patient was allocated to the

category said patient was in the most. The above categories of adherence and allocation process are in accordance with the protocol of an as of yet unpublished study by Schrijver et al.[18] The categories are not ranked. While one would expect patients in the "optimal treatment" category to perform better than the others on some health outcomes as, as was mentioned in the introduction, adherence is in some other studies associated with better health outcomes, it is difficult to determine which category of adherence one would expect to perform worse: the "significant delay or no treatment" category or the "treatment outside actual exacerbation period" category. This because while treating with oral prednisolone is said to improve health outcomes, prednisolone has side effects such as depression and anxiety, and thus unnecessary treatment might not help improve or maybe even worsen patients' health outcomes. [19,20]

Data on patient adherence was collected retrospectively from the symptom dairies, using the start date of the exacerbation and the start date of prednisolone. [16]

Baseline characteristics

To check the comparability of the adherence categories, and to help establish possible confounding variables, a table of baseline characteristics was made. The selection of these baseline characteristics was confined to what was studied in both the COPE-II and the COPE-III study. All baseline variables which were known from both the COPE-II and the COPE-III study populations were included. The following variables were considered: age, gender, Body Mass Index (BMI), smoking status, Forced Expiratory Volume $(FEV)_1$%-predicted, dyspnoea as determined by the modified Medical Research Council (mMRC), patients' Global Initiative for Chronic Obstructive Lung Disease[1] (GOLD) GOLD-stage, comorbidities (ischaemic heart disease, heart failure, diabetes mellitus, anxiety and depression), COPE-study patients were originally enrolled in, patients' level of education, employment status, and whether patients were living together. As anxiety and depression were not collected as variables as such in the COPE-II study, whether patients from the COPE-II study were considered as someone with anxiety or depression was determined for the current study by the HADS-scores at baseline. For both anxiety and depression, patients with a HADS-score of 11 or higher were considered as patients with anxiety or depression. The same cut-off of 11 or higher was used in the COPE-III study. [21] Thus the data-set could be completed on these variales using the same criteria for all patients.

Primary outcome

COPD exacerbations.

The most important outcomes that are evaluated in this study are those related to COPD exacerbations. The number of COPD exacerbations, the total number of COPD exacerbation days during follow-up and the duration per COPD exacerbation were studied. Based on the studies [3,13] discussed in the introduction, it is expected that taking prednisolone according to the COPD exacerbation action plan faster would shorten the duration of an exacerbation. In the COPE-III study a reduction in the duration of COPD exacerbations was found.[12]

The duration of a COPD exacerbation was defined as the number of days between the start and the end of the exacerbation. [7,12] The start was defined as the first of two or more consecutive days in which two major symptoms or one major and one minor symptom were significantly worse than normal. The end was the first day of either three consecutive days in which the patient was in normal health or seven days in a row in which a patient experienced no or only a slight increase in symptoms compared to normal, provided there was no fever or change in sputum colour. Dyspnoea, sputum production and sputum colour were considered to be major symptoms.[12] Cough, wheeze and a body temperature higher than 38,5 degrees Celsius were considered to be minor symptoms. This

definition of the start and end date of exacerbations was the same as in the COPE-II and the COPE-III study. [7,12]

Secondary outcomes

Hospital visits

As discussed in the introduction, evidence on the effect of adherence to COPD exacerbation action plans on hospital visits and admissions is conflicting. In both the COPE-II and COPE-III study hospital visits and admissions were recorded. In COPE-II a reduction in hospital visits in the action plan group was found and in COPE-III a reduction in the risk of respiratory related hospital admissions in the action plan group was found.[7,12] Thus, it is relevant to study the effect of the level of adherence on unplanned hospital visits. The number of hospitalisations, the number of days spent in hospital and the number of patients who were hospitalized at least once during the follow-up were determined per patient and grouped per category of adherence.

Mortality

Mortality will be studied as evidence on mortality in self-management programs for COPD is conflicting, with some studies being ended prematurely due to an unexpected higher death rate in the intervention group.[10] Therefore, it is relevant to determine whether any difference can be found in mortality between different levels of adherence to the COPD exacerbation action plans in patients. Mortality was measured using the data on withdrawals from the COPE-II and COPE-III studies, as those who died during the follow-up of both source studies were withdrawn as a consequence. The mortality per category of adherence was assessed in order to determine the risk per category.

Anxiety and depression

The effect of adherence to the COPD exacerbation action plan on anxiety and depression symptoms was measured in the change in HADS-score. The HADS-score is a questionnaire which can give scores between 0 and 21 for both anxiety and depression separately or between 0 and 42 for anxiety and depression combined.[22] HADS scores were determined at baseline and at twelve months.[7,12] The change in HADS-score was determined per patient, by taking the score at 12 month follow-up minus the score at baseline, in order to calculate the average change in HADS-score per category of adherence. These average differences were compared in statistical analysis.

Health Related Quality of Life HRQoL

In order to assess whether adherence to a COPD exacerbation action plan influences the HRQoL experienced by a patient, a comparison between the average difference in HRQoL per category of adherence was made. This was done by calculating the difference between HRQoL at inclusion and at 12 months per patient, by deducting the baseline score from the 12-month follow-up score.

In both the COPE-II and COPE-III study researchers used the Chronic Respiratory Questionnaire (CRQ) to determine HRQoL. This is a twenty-item questionnaire with questions regarding the impairment aspects of COPD causes on activities and emotions. This questionnaire has 4 domains: dyspnoea, fatigue, emotional functions and mastery. [23] The higher the score on the CRQ, the higher the quality of life. In this study, the average difference in score on CRQ per category was calculated in order to be compared in statistical analysis. In order to assess whether adherence to COPD exacerbation action plans influences HRQoL the difference in CRQ-score between baseline and twelve-month follow-up was calculated per CRQ-domain.

Statistical analyses

Statistical analysis was done using SPSS for Windows version 25. In the analysis of baseline variables, a p-value of <0.10 was considered significant. In all analyses of health outcomes, a p-value of <0.05 was considered significant. [24] Continuous variables were analysed using ANOVA when normally distributed and using Kruskal Wallis-tests when not normally distributed. Post-hoc analysis was done using the Tukey SD or Holm-Bonferroni correction, dependent on the normality of the distribution, which was determined visually using histograms. Categorial variables were assessed using χ^2-tests or Fishers exact test.

The following baseline characteristics were treated as binary variables: gender, smoking status, comorbidities, source study patients were originally enrolled in, employment status and whether patients were living together. GOLD-stage and level of education were considered categorial variables. Age, FEV 1%-predicted, dyspnoea-score and BMI were treated as continuous variables. All exacerbation outcomes were treated as continuous, as were number of hospital visits, number of days spent in hospital and outcomes regarding anxiety, depression and HRQoL. Mortality and number of patients who had to be admitted to hospital at least once were considered binary outcomes.

Confounding was assessed using linear regression. When the ANOVA or Kruskal Wallis analysis showed a significant difference between categories of adherence, linear regression was performed in order to determine whether this significant difference was there because of a confounding baseline variable. A separate model was determined for each outcome. When all four categories of adherence were part of the analysis, the “treatment outside actual exacerbation period” category was used as the reference category. When three categories of adherence were analysed, the “significant delay or no treatment” category was used as the reference category. All other categories were added to the model as binary variables using dummy variables. At first, all possible confounding baseline variables, e.g. all baseline variables where initial analysis showed a between-group difference significant at p<0.10 level and showed a significant correlation with the outcome in question, were added to the model. Then, the variable with the highest p-value was removed from the model. This was done repeatedly, until either all p-values were significant at p<0.05 or the removal of a variable led to the coefficients of adherence categories changing more than 10%, or only the categories of adherence remained. For non-normally distributed data, models were made both with non-transformed data and ln-transformed data, choosing the best fit for each outcome based on R-squared and normality of the distribution of residuals. When a variable was in the final model, it was considered a confounder. The final models are reported in the results section.

Ethical considerations

No new data was collected. The data used has been collected in two RCT studies, for which participants gave informed consent. The research protocols for both these RCT’s have been approved by medical ethical committees.[7,12] In case of the COPE-II study approval was given by the ethical committee of the Medisch Spectrum Twente hospital in Enschede. In case of the COPE-III study approval was given by the Medical Ethical Committee Twente, The Netherlands and the Southern Adelaide Clinical Human Research Ethics Committee, Australia.

The most important consideration for this study is whether it is allowed to use the data from the COPE-II and III studies for this new study. Patients gave informed consent for the use of their data in the COPE-II and COPE-III study.[7,12]

Ethical approval for this study has been obtained from the Ethics Committee of the faculty of Behavioural and Management Sciences at the University of Twente.

Results

Patient groups

In total, 145 patients from the self-treatment groups of the COPE-II (n=64) and COPE-III (n=81) studies were included in this analysis. Patients had been allocated to one of four categories of adherence: “significant delay or no treatment” (n=46), “suboptimal treatment” (n=17), “optimal treatment” (n=38) and “treatment outside the actual exacerbation” period category (n=44). Of all patients included in this analysis, 69.7% had at least one comorbidity.

Baseline characteristics

In order to assess comparability of the patients in the aforementioned four categories of adherence, several baseline characteristics were compared. As can be seen in table 2a, the four adherence categories appear to be comparable in terms of age, BMI, FEV_1% predicted, GOLD-stage, gender, smoking status, level of education, employment-status, living together, number of exacerbations and hospitalisations in the previous year and the percentage of people who had anxiety, depression and diabetes. Significant differences ($p<0.10$) between groups were found for dyspnoea score (mMRC-score), source of the study, i.e. the COPE study in which a patient was originally included, and cardiac disease. As the “treatment outside actual exacerbation period” category of adherence differed significantly from the other categories in the number of exacerbations, separate analyses were also performed comparing the baseline characteristics between the “significant delay or no treatment” category, the “suboptimal treatment” category and the “optimal treatment” category. This required insight in the comparability of baseline characteristics between these three categories. Only the difference in dyspnoea score remained significant ($p<0.10$) when the baseline variables were compared between the “significant delay or no treatment” category the “suboptimal treatment” category and the “optimal treatment” category. The results of this analysis of baseline variables can be seen in table 2b.

In the analysis of health outcomes between all four categories of adherence, cardiac disease at baseline, the COPE-study patients were initially enrolled in (source study) and dyspnoea, as determined by the mMRC score, were treated as possible confounders when they also influenced the outcome in question. In analysis of outcomes between the ”significant delay or no treatment”-category, the “suboptimal treatment” category and the “optimal treatment” category dyspnoea, as determined by the mMRC score, was treated as a possible confounder if it also influenced the outcome in question.

Table 2a: Baseline characteristics of all four patient categories of adherence.

Characteristic	Significant delay/ no treatment (N=46)	Suboptimal treatment (N=17)	Optimal treatment (N=38)	Treatment outside actual exacerbation period (N=44)	Asymptotic two-sided Significance of difference
Age[a]	65,6; 9.87	66,5; 8.24	65.3; 9.67	68.1; 7.11	p= 0.41[#]
BMI[b]	27.5; 23.4-31.8	29.3; 26.6-32.5	25.9; 23.4-30.7	27.8; 23.6-31.9	p= 0.35[*]
Gender (% male)	47.8	64.7	60.5	72.7	p= 0.11[^]
Currently smoking (%yes)	32.6	17.6	28.9	22.7	p =0.58[^]
COPE-II/III[**] (%COPE-II)	47.8	70.6	47.4	27.3	**p = 0.016[^]**
Cardiac disease (% yes)	28.3	41.2	39.5	61.4	**p = 0.016[^]**
Diabetes (%yes)	29.2	80.0	45.0	31.1	p= 0.14[@]
Anxiety (%yes)	23.9	11.8	13.2	25.0	p = 0.42[^]
Depression (%yes)	28.3	5.9	26.3	18.2	p= 0.23[^]
GOLD-stage[1] (% II) (% III) (% IV)	 54.3 34.8 10.9	 52.9 41.2 5.9	 59.9 28.9 13.2	 43.2 50.0 6.8	p=0.59[@]
FEV_1 (%) predicted[a]	52.2; 17.24	51.8; 14.86	52.5; 16.37	48.8; 14.97	p = 0.73[#]
mMRC-score[a] [25]	2.18; 1.07	1.65; 1.17	1.65; 1.16	1.82; 0.87	**p=0.09[*]**
Number of exacerbations 2 year prior to inclusion in source study [b]	3; 2-4	4; 2-5	3.5; 3-5	3; 2-4	p= 0.33[*]
Number of hospitalisations 1 year prior to inclusion in source study[b]	0.8; 0-1	0.8; 0-1	0.7; 0-1	0.7; 0-1	p= 0.47[*]
Employment (%yes)	26.1	29.4	18.9	18.2	p= 0.67[^]
Living together (%yes)	65.2	70.6	60.5	65.9	p= 0.90[^]
Education level (% low) (% middle) (% high)	 52.2 37.0 10.9	 47.1 12.1 11.8	 50.0 27.6 7.9	 50.0 31.0 9.1	p= 0.99[@]

Significant (p<0.10) values are printed in **bold**. [a] presented is the mean (standard deviation) [b] presented is the median (25th 75th percentile) Abbreviations: BMI= Body Mass Index. GOLD = Global Initiative for Chronic Obstructive Lung Disease FEV1 =Forced Expiratory Volume in 1 second. mMRC = modified Medical Research Council **study patient was originally included in. *Kruskal Wallis test. @ Fishers exact test. ^ χ2-tests # ANOVA

Table 2b Baseline characteristics of three patient categories of adherence.

Characteristic	Significant delay/ no treatment (N=46)	Suboptimal treatment (N=17)	Optimal treatment (N=38)	Significance of difference between groups
Age[a]	65,6; 9.87	66,5; 8.24	65.3; 9.67	P= 0.88 #
BMI[b]	27.5; 23.4-31.8	29.3; 26.6-32.5	25.9; 23.4-30.7	P= 0.20*
Gender (% male)	47.8	64.7	60.5	P= 0.36 ^
Currently smoking (%yes)	32.6	17.6	28.9	P= 0.54@
COPE-II/III** (%COPE-II)	47.8	70.6	47.4	P= 0.22^
Cardiac disease (% yes)	28.3	41.2	39.5	P= 0.46^
Diabetes (%yes)	29.2	80.0	45.0	P= 0.10@
Anxiety (%yes)	23.9	11.8	13.2	P= 0.40 @
Depression (%yes)	28.3	5.9	26.3	P= 0.16+
GOLD-stage[1] (% II) (% III) (% IV)	 54.3 34.8 10.9	 52.9 41.2 5.9	 59.9 28.9 13.2	P=0.89^
FEV_1(%) [a]predicted	52.2; 17.24	51.8; 14.86	52.5; 16.37	P= 0.99 #
mMRC-score [a] [25]	2.18; 1.07	1.65; 1.17	1.65; 1.16	**P=0.06***
Number of exacerbations 2 year prior to inclusion in source study[b]	3; 2-4	4; 2-5	3.5; 3-5	P= 0.18*
Number of hospitalisations 1 year prior to inclusion in source study[b]	0.8; 0-1	0.8; 0-1	0.7; 0-1	P= 0.29*
Employment (%yes)	26.1	29.4	18.9	P= 0.63@
Living together (%yes)	65.2	70.6	60.5	P= 0.76^
Education level (% low) (% middle) (% high)	 52.2 37.0 10.9	 47.1 12.1 11.8	 50.0 27.6 7.9	P= 0.96@

Health outcomes

The results of the analyses of health outcomes are shown in table 3. As can be seen significant results were found regarding the COPD exacerbation characteristics and HRQoL. COPD exacerbations were shorter in the "Suboptimal" and "Optimal" treatment categories than in the "Significant delay or no treatment" category. The number of COPD exacerbation days was also lower in the "Suboptimal" and "Optimal" treatment categories than in the "Significant delay or no treatment" category. No differences were found in mortality or hospitalisations.

Table 3. Results of primary analysis of exacerbation characteristics, hospital visits, mortality, anxiety, depression and HRQoL.

Outcome	Significant delay or no treatment (N=46)	Suboptimal treatment (N=17)	Optimal treatment (N=38)	Treatment outside actual exacerbation period (N=44)	Significance of between-group differences
Number of COPD exacerbations [a]	3; 1.8-6.0	3; 2-5	3; 2-5	1;0-2	**P<0.01***
Number of COPD exacerbation days[a]	52.5;19.5-92.0	29; 10.5-45.0	25; 11.5-43.5	3; 3-16.5	**P<0.01***
Duration per COPD exacerbation[a]	11.7;8.4-23.9	7; 4.9-9.8	7.2; 5.6-10.1	3.0; 0-4.7	**P<0.01***
Number of patients died during follow-up	2	1	1	0	P= 0.47@
Number of hospitalisations [b]	0.83; 1.40	0.24; 0.56	0.68;1.5	0.45;0.82	P= 0.31*
Number of all cause hospitalisation days [b]	8,4; 15.11	1.47; 3.66	6.7;14.56	3.0;6.33	P= 0.24*
Number of patients who had at least one hospitalisation during follow-up	18	3	10	13	P= 0.36^
Difference in HADS-A score [ac] [26]	-2.0; -3.0-1.0	0.0; -2.8;1.8	0.0; -1.8-1.0	0.0; -3.0-1.0	P= 0.27@
Difference in HADS-D score [bc] [26]	-0.76; 2.56	-1.06; 3.07	0.28; 2.52	-0.73;3.16	P= 0.31 #
Difference in CRQ [27]dyspnoea score[bd]	-0.55;1.13	0.16; 0.62	-0.24; 0.86	0.25;1.12	**P= 0.006** #
Difference in CRQ [27]fatigue score[bd]	-0.11; 1.17	-0.03; 0.87	0.05; 1.03	0.09; 1.12	P= 0.86 #
Difference in CRQ [27]emotions score[bd]	0.31; 0.98	0.16; 0.71	-0.11; 1.00	0.05;1.05	P = 0.36 #
Difference in CRQ [27]mastery score [bd]	0.43; 1.05	0.30; 0.67	0.0-; 0.76	0.24; 0.87	P= 0.25 #

Significant results are printed in **bold.** [a] presented data are median; 25th 75th percentile. [b]presented data are mean; standard deviation. [c]differences are calculated by 12M-baseline. Scores above zero indicate deteriorations. [d] differences are calculated by 12M - baseline. Scores above zero indicate improvements. Abbreviations: HADS= Hospital Anxiety and Depression Scale. CRQ= Chronic Respiratory Questionnaire. *Kruskal Wallis test. @ Fishers exact test. ^ χ2-tests # ANOVA

COPD exacerbations

In order to analyse COPD exacerbations three outcomes were investigated: the number of COPD exacerbations per patient, the total number of COPD exacerbation days per patient and the average duration per COPD exacerbation per patient. When analysing all four categories, significant differences were found between the "treatment outside actual exacerbation category" and all other categories of adherence on COPD exacerbation characteristics. (table 3) In order to assess possible confounding by differing baseline variables and to determine the size of the effect of different

categories of adherence to COPD exacerbation action plans on COPD exacerbation outcomes, linear regression was performed for all analysis of COPD exacerbation characteristics. The reference category was "treatment outside actual exacerbation period". The results can be found in table 4a-c. The R-squared varied between 14-25%.

Table 4a. Linear regression model of number of COPD exacerbations compared between all four categories of adherence to COPD exacerbation action plans.

Variable	β (95% Confidence Interval)	p-value
Constant	**2.1 (91.1-3.1)**	**<0.01**
Significant delay or no treatment	**1.8 (0.8-2.9)**	**<0.01**
Suboptimal treatment	**1.6 (0.2-3.1)**	**0.02**
Optimal treatment	**1.9 (0.8-2.9)**	**<0.01**
COPE-II/III	-0.5 (-1.4-0.3)	0.20

Significant results are printed in **bold**. Reference category: "treatment outside actual exacerbation period". The data in this model are not transformed. The R-squared is 14%.

Initially the variable cardiac disease at baseline was included in this model as well, but it was removed as omitting it did not change the coefficients with more than 10%, and thus it was not considered a confounder. The model in table 4a shows that the predicted number of exacerbations is lower in the "treatment outside the actual exacerbation period" category, the difference between this category and each other category of adherence being almost two exacerbations. Source study was considered a confounder, with the model predicting 0.5 less exacerbations for patients in the COPE-III study than patients in the COPE-II study.

Table 4b. Linear regression model of number of COPD exacerbation days compared between all four categories of adherence to COPD exacerbation action plans.

Variable	β (95% Confidence Interval)	p-value
Constant	5.7 (-13.7 -25.1)	0.56
Significant delay or no treatment	**52.3 (33.4-71.2)**	**<0.01**
Suboptimal treatment	16.5 (-8.7 – 41.8)	0.20
Optimal treatment	**19.8 (0.6 – 39.0)**	**0.04**
mMRC*-score [25]at baseline	6.6 (-0.8-14.0)	0.08
COPE-II/COPE-III	-10.0 (-26.5 – 6.4)	0.23

Significant results are printed in **bold**. Reference category: "treatment outside actual exacerbation period". The data in this model are not transformed. The R-squared is 25%. * modified Medical Research Council.

In the model in table 4b, cardiac disease at baseline was initially included, but it was not a significant confounder. The model predicts that patients in the "significant delay or no treatment" category experience 52.3 more COPD exacerbation days over a twelve-month follow-up than patients in the "treatment outside actual exacerbation period" category. The predicted number of exacerbation days over a twelve-month follow-up for patients in the "significant delay or no treatment category" is 58. For patients in the "optimal treatment category" this number is 25.5 days.

Table 4c. Linear regression model of duration of COPD exacerbations compared between all four categories of adherence to COPD exacerbation action plans.

Variable	β (95% Confidence Interval)	p-value
Constant	**1.7 (1.4-2.1)**	**<0.01**
Significant delay or no treatment	**1.0 (0.6-1.4)**	**<0.01**
Suboptimal treatment	0.3 (-0.2 – 0.8)	0.22
Optimal treatment	0.3 (-0.1 – 0.8)	0.10
Cardiac disease at baseline	-0.2 (-0.5 – 0.1)	0.17

Significant results are printed in **bold**. Reference category: "treatment outside actual exacerbation period". The data in this model are ln-transformed. The R-squared is 25%.

The model in table 4c shows the ln-transformed coefficients. Using this as a model and transforming the outcomes back suggests that the predicted duration of a COPD exacerbation in the "significant delay or no treatment" category is 9.4 days longer than in the "treatment outside actual exacerbation category", the predicted duration of a COPD exacerbation for a patient in the "significant delay or no treatment category" with no cardiac disease at baseline being 14.9 days compared to 5.5 days in the "treatment outside actual exacerbation period" category. The coefficients of the other categories of adherence do not reach statistical significance.

The difference found when comparing the COPD exacerbation characteristics between al four categories of adherence included the number of COPD exacerbations. One would not expect the number of COPD exacerbations to be influenced by adherence to the COPD exacerbation action plan, as the action plan only instructs patients to start self-treatment when they experience a COPD exacerbation.[12] Because of this difference, the other three categories were then analysed separately for all COPD exacerbation characteristics.

This separate analysis (table 5) showed significant differences among the three categories of adherence in both the number of COPD exacerbation days ($p<0.01$) and the duration per COPD exacerbation ($p<0.01$). The "significant delay or no treatment"-category had the highest number of COPD exacerbation days (median 52.5 Interquartile Range (IQR): 19.5-92.0) and the longest average duration per COPD exacerbation (median 11.7 IQR: 8.4-23.9). The number of COPD exacerbations did not differ significantly in this analysis. Post-hoc analysis using paired Mann-Whitney U tests with alphas adjusted using the Holm-Bonferroni method [28,29] suggest that the "suboptimal" and the "optimal" categories of adherence do not differ significantly from each other, but both differ significantly from the "significant delay or no treatment" category of adherence in duration per COPD exacerbation. The "optimal treatment" category also differs significantly from the "significant delay or no treatment" category in the number of COPD exacerbation days. The "suboptimal treatment" category does not. COPD exacerbations in the "suboptimal" and "optimal" treatment category are significantly shorter than those experienced by patients in the "significant delay or no treatment category".

Table 5. Significance of differences between three categories of adherence.

Outcome (median; 25th-75th percentile)	Significant delay or no treatment (N=46)	Suboptimal treatment (N=17)	Optimal treatment (N=38)	Asymptotic significance
Number of COPD exacerbations	3; 1.8-6.0	3; 2-5	3; 2-5	P= 0.99
Number of COPD exacerbation days	52.5;19.5-92.0	29; 10.5-45.0	25; 11.5-43.5	**P<0.01**
Duration per COPD exacerbation	11.7;8.4-23.9	7; 4.9-9.8	7.2; 5.6-10.1	**P<0.01**

Significant results are printed in **bold.** Kruskal Wallis analysis.

Linear regression was also performed to determine the effect size and the role of possible confounding by mMRC dyspnoea score in this separate analysis of three categories of adherence. The results can be found in table 6a-c. The reference category in these models is the "significant delay or no treatment" category. R-squared values varied between 0-17%

Table 6a. Linear regression model of number of COPD exacerbations compared between three categories of adherence to COPD exacerbation action plans.

Variable	β (95% Confidence Interval)	p-value
Constant	**3.0 (2.9-4.4)**	**<0.01**
Suboptimal treatment	-0.1 (-1.5-1.3)	0.93
Optimal treatment	0.0 (-1.1-1.1)	0.95

Significant results are printed in **bold.** Reference category: "Significant delay or no treatment". The data in this model are not transformed. The R-squared is 0%.

The model in table 6a shows that the number of exacerbations does not differ significantly between the "significant delay or no treatment category" and the "suboptimal treatment" and "optimal treatment" categories. The R-squared value of this model is very low, which also shows that the category of adherence cannot be used to explain the variance in COPD exacerbation frequency among these categories.

Table 6b. Linear regression model of number of COPD exacerbation days compared between three categories of adherence to COPD exacerbation action plans.

Variable	β (95% Confidence Interval)	p-value
Constant	**54.0 (29.6-78.3)**	**<0.01**
Suboptimal treatment	**-33.8 (-62.1 - -5.5)**	**0.02**
Optimal treatment	**-32.8(-54.9 - -10.8)**	**<0.01**
mMRC*-score[25] at baseline	6.1 (-2.8– 15.0)	0.18

Significant results are printed in **bold.** Reference category: "Significant delay or no treatment". The data in this model are not transformed. The R-squared is 14%. * modified Medical Research Council

The model in table 6b predicts the number of COPD exacerbation days for patients in the "suboptimal treatment" and "optimal treatment" categories to be around 33 days less than patients in the "significant delay or no treatment" category. The mMRC-score is a confounder for which this model corrects.

Table 6c. Linear regression model of duration of COPD exacerbations compared between three categories of adherence to COPD exacerbation action plans.

Variable	β (95% Confidence Interval)	p-value
Constant	**2.7 (2.5-2.9)**	**<0.01**
Suboptimal treatment	**-0.8 (-1.2 ; -0.3)**	**<0.01**
Optimal treatment	**-0.7 (-1.1 ; -0.3)**	**<0.01**

Significant results are printed in **bold.** Reference category: "Significant delay or no treatment". The data in this model are ln-transformed. The R-squared is 17%.

The model in table 6c shows ln-transformed coefficients. When transforming the outcomes back the model predicts that COPD exacerbations last 6.6 days in the "suboptimal treatment category" and 7.4 days in the "optimal treatment" category, both of these being around 50% shorter than the 14.9 days the model predicts for patients in the "significant delay or no treatment" category.

Hospitalisations

Hospitalisations were assessed in three ways: the number of hospitalisations per category, the number of patients who had at least one hospitalisation per category and the number of days spent in hospital per category. No significant difference in number of hospitalisations between all four of

the defined categories of adherence to COPD exacerbation action plans was found. In the number of patients who had to be admitted to hospital at least once during follow-up no significant differences were found. No significant differences per category of adherence in the number of days spent in hospital were found.

Mortality

In total, four patients died during the follow-up of their respective studies. Of these four, two patients were in the "significant delay or no treatment"-category and one in both the "suboptimal" and "optimal"-adherence categories. No patients from the "treatment outside actual exacerbation period"-category died during the follow-up. Differences in mortality were analysed using Fishers exact. No significant difference in mortality was found using Fishers exact test. In this study, mortality does not seem to be influenced by the categories of adherence to COPD exacerbation action plans.

Anxiety and Depression

The difference in HADS-A and HADS-D scores were calculated per patient. Based on these histograms, distributions for HADS-A were considered not normal. No significant difference between all four categories of adherence to COPD exacerbation action plans in change in HADS-scores was observed. No significant difference in the change in HADS-D score was found between groups. On average patients' anxiety and/or depression did not worsen or improve significantly during follow-up, regardless of what category of adherence patients were in.

Health Related Quality of Life

Health Related Quality of Life was measured in both source studies using the CRQ. A significant difference ($p< 0.01$) was found in the dyspnoea domain, when all four categories of adherence to COPD exacerbation action plans were analysed. Post-hoc analysis showed that patients in the "treatment outside actual exacerbation period" group improved significantly more on the dyspnoea domain than patients in the "significant delay or no treatment" group. On average the CRQ dyspnoea score in the "significant delay or no treatment" -group worsened with -0.55 while the average change in CRQ dyspnoea score in the "treatment outside actual exacerbation period"-group was +0.25. No significant differences were found in the other domains. The p-values were 0.25 for CRQ mastery, 0.86 for CRQ fatigue and 0.36 for CRQ emotions.

In order to determine whether the significant difference in improvement in the dyspnoea-domain of the CRQ could be caused by possible confounding variables, linear regression was performed. The model, with an R-squared of 18.4% suggested significant influence of the source study patients came from (p-value <0.05). However, the influence of both the "significant delay or no treatment"-category and the "optimal treatment" category still remained significant at $p<0.01$ level. Further results can be found in table 7.

Table 7. Linear regression model of improvement in dyspnoea-domain of CRQ*.

Variable	β (95% Confidence Interval)	p-value
constant	**0.66 (0.24-1.08)**	**<0.01**
Significant delay or no treatment	**-0.96 (-1.42; - 0.50)**	**<0.01**
Suboptimal treatment	-0.33 (-0.93-0.27)	0.28
Optimal treatment	**-0.61 (-1.08-; -0.14)**	**0.01**
COPE-II/III	**-0.56 (-0.93; -0.19)**	**<0.01**

Significant results are printed in **bold**. Reference category: "treatment outside actual exacerbation period" R-squared: 18%. *Chronic Respiratory Questionnaire.

The difference in CRQ-dyspnoea scores was 0.96 lower in the “significant delay or no treatment” category than in the “treatment outside of actual exacerbation period” category. In the “optimal treatment” category the difference was 0.61 less than in the “treatment outside actual exacerbation” category. As a positive value means an improvement on HRQoL in this domain, this suggest that patients in the “significant delay or no treatment” category and the “optimal treatment” category experienced worse results on their HRQoL in this domain than patients in the “treatment outside actual exacerbation period” category. This model predicts a difference of -0.3 between 12 months follow-up and baseline for patients in the “significant delay or no treatment” category who were originally included in the COPE-II study, while patients from the COPE-II study in the “optimal treatment” category are predicted a difference of 0.05 between 12 months follow-up and baseline. Adding the confounding variable of the source study patients were originally included in alters the results found in the initial ANOVA. The predicted deterioration in CRQ dyspnoea score for patients from the COPE-II study in the “significant delay or no treatment” category is -0.3 which is a better result than this category appeared to score without correcting for possible confounding. For patients in the same category who were originally included in the COPE-III study, however, the predicted deterioration in CRQ-dyspnoea in the “significant delay or no treatment” category is 0.86, which is worse than the category appeared to score without correcting for possible confounding.

Discussion

This study was a retrospective cohort study, focussed on the effect of adherence to COPD exacerbation action plans on health outcomes. In this study patients in the "suboptimal" and "optimal" treatment categories experienced shorter COPD exacerbations and less COPD exacerbation days per year than patients in the "significant delay or no treatment" category.

Discussion of results

Number of COPD exacerbations

The number of exacerbations did not differ significantly between the "optimal", "suboptimal" and "significant delay or no treatment" categories of adherences. This is in line with what was expected a priori, as the number of exacerbations did not differ between the self-management group and the control group in the COPE-III study either. [12] After all, the COPD exacerbation action plans were only triggered once patients experienced a COPD exacerbation, and thus the opportunity for adherence did not arise before then. One cannot follow instructions correctly, before the event triggering the instructions takes place.

Number of COPD exacerbation days

Analysis showed a significant difference in the total number of COPD exacerbation days between categories of adherence to COPD action plans. Analysis showed that patients in the "suboptimal adherence" and the "optimal adherence" categories had 32.8-33.8 fewer exacerbation days during the twelve month follow up than patients in the "significant delay or no treatment" category. This might be because patients from the "suboptimal" and "optimal treatment" categories used oral prednisolone during a COPD exacerbation, which improves health outcomes. [19]

Duration of COPD exacerbations

The duration of COPD exacerbations was significantly less in the "suboptimal adherence" and the "optimal adherence" category than in the "significant delay or no treatment" category. Duration of COPD exacerbation in the "suboptimal treatment" category was predicted 7.4 days shorter in the model found in this study. The duration of COPD exacerbations in the "optimal treatment" category was predicted to be 6.6 days shorter. The number of days by which adherence appears to shorten COPD exacerbations in this study is close to the reduction in exacerbation duration reported in the studies by Bischof et al.[3] and Farias et al. .[13] In both of these studies, the effect of being non-adherent or adherent to COPD exacerbation action plans on the duration of COPD exacerbations was studied. While the effect of different timings of adherence to COPD-exacerbation action plans was not studied in either of these studies, the outcomes are still comparable to this current study. Their definition of adherence has a time limit of 72 hours, which means that patients in the "optimal" and "suboptimal" treatment categories from this current study would likely be considered "adherent" in the studies by Bischof et al.[3] and Farias et al.[13] In the study by Bischoff et al.[3] it was found that being adherent reduced the duration of exacerbations with 5.1 days, which they considered to be clinically relevant. Based on the average duration of a COPD exacerbation reported in the control group COPE-III study, which was 7 days, and the average duration of a COPD exacerbation reported in a 2004 study by Wilkinson et al.[19] which was 10.7 days, I feel that the reductions in COPD exacerbation duration found in this study (6.6-7.4 days) could be seen as clinically relevant. The "suboptimal adherence" and "optimal adherence" categories did not, however, differ significantly from each other in COPD exacerbation duration. This is interesting, as it suggests that starting a course of oral prednisolone anywhere between two days prior and after the start of a COPD exacerbation is equally effective in limiting the duration of COPD exacerbations. The findings in this

study suggest that as long as one starts a course of oral prednisolone within two days of the start of a COPD exacerbation, starting sooner or later does not seem to change the duration of COPD exacerbations.

Hospital visits

The analysis performed in this study showed no significant difference in the number of hospital visits, the number of days spent in hospital or the risk of hospital visits between categories of adherence. This is in accordance with the results of the study by Bischoff et al.[3], who also did not find a difference in hospital visits between adherent and non-adherent patients. In the Cochrane systematic review on COPD self-management interventions by Lenferink et al. no significant effect of self-management interventions on all-cause hospitalisations was found either. [10] In a review on COPD self-management interventions it was also concluded that the evidence on the effects of COPD self-management on hospitalisations is inconclusive. [30] However, the findings in this study are not in accordance with the results of the study by Choi et al.[14] in which adherence was associated with less hospitalisations. However, Choi et al.[14] used self-reported adherence, which is known to over-report adherence to medication. [15]

Mortality

No significant difference in mortality was found. This is in accordance with literature on COPD exacerbation action plans.[12] To my knowledge, this is the first study studying the effect of adherence to COPD exacerbation action plans on mortality. However, this study was not powered to detect small differences in mortality. Therefore, these results cannot be generalized to the population of COPD patients.

Anxiety and depression

There was also no significant difference in anxiety and depression. This is not in accordance with the study by Choi et al.[14], who reported a positive effect of adherence to COPD exacerbation action plans on anxiety and depression. This difference can perhaps be explained as the study by Choi et al.[14] was cross-sectional, while in this study it was possible to analyse whether patients' HADS-scores improved or deteriorated during the follow-up period of their respective studies. As the study by Choi et al. is cross-sectional it is not possible to determine whether better HADS-scores contribute to better adherence or whether better adherence contributes to better HADS-scores. Depression has been described as a risk factor for non-adherence in general. [31]

Health Related Quality of Life

In HRQoL, no difference between categories of adherence to COPD exacerbation action plans was found in the domain's emotions, fatigue and mastery. A significant difference of 0.96 was found between the "treatment outside actual exacerbation period" category and the "significant delay or no treatment" category. Linear regression in order to assess the role of confounding variables also suggested a significant difference of 0.61 between the "optimal treatment" and the "treatment outside actual exacerbation period" categories. These differences exceed the mark for clinical relevance, which has been set at an improvement or deterioration of more than 0.5 point per domain.[32] More exacerbation-free time, i.e. less time per year spent while experiencing a COPD exacerbation, has been linked to better HRQoL.[33] In the linear regression analysis, both the "optimal treatment" and the "significant delay or no treatment" categories appear to have a significantly higher number of COPD exacerbation days than the "treatment outside actual exacerbation period" category. The lower level of exacerbation free time in these categories might

be an explanation for their worse performance in the dyspnoea domain in the CRQ. The study patients originally were included in was a significant confounder in the analysis of the difference in CRQ dyspnoea scores. Patients from the COPE-III study appeared to perform worse. Cardiac disease and mMRC dyspnoea score at baseline were no significant confounder in the analysis of this variable which makes them less likely to be the mechanism through which this confounder works. No other comorbidity differed between the four categories of adherence. We have not been able to find an explanation for this confounder. Analysing the results for each COPE-study separately might have provided more insight in the working of this confounder, however, sample sizes would have been quite low, which would reduce the precision of the results found.

Treatment outside actual exacerbation category versus other categories

As mentioned in the results, the decision was made to perform a separate analysis of the COPD exacerbation characteristics in which the "Treatment outside the actual exacerbation period" category was excluded, due to the different character of this category. This different character might possibly be explained with the following.

The lower number of COPD exacerbations in the "Treatment outside actual exacerbation period" category, despite the fact that one would not expect adherence to COPD exacerbation action plans to influence this, might be due to its inclusion criteria. In order to be included in the "significant delay or no treatment", "suboptimal treatment" and "optimal treatment" categories, patients had to have had at least one COPD exacerbation during the follow-up. However, taking a course of oral prednisolone, whether this was during a COPD exacerbation or not, was enough to be included in the "Treatment outside actual exacerbation period". [18] Thus, one could have been included in the "treatment outside actual exacerbation period" category without having had a COPD exacerbation during follow-up. This is also visible in '0' being the 25th percentile of the number of COPD exacerbations in this category. The differences in COPD exacerbation characteristics between the "treatment outside the actual exacerbation period" category and the other categories of adherence could perhaps be partially explained as more patients in this category were originally included in the COPE-III study and more patients in this category of adherence had a cardiac disease at baseline. Symptoms of cardiac exacerbations and COPD exacerbations can overlap. [6] Thus it might be that patients mistook their cardiac exacerbations for a COPD exacerbation without actually experiencing a COPD exacerbation. Also, oral prednisolone can be prescribed for multiple reasons.[20] Thus, it might be that patients started a course of oral prednisolone for a non-COPD related reason, and it led to inclusion in this category.

To my knowledge this is the first study to analyse the effects of this form of adherence to COPD exacerbation action plans separately. Because of this lack of data, and the other explanations for the results found given in this discussion, I feel that, while being in the "treatment outside actual exacerbation category" was not related to any significant negative effects compared to other categories of adherence in this study, it cannot be concluded that treating outside the actual exacerbation period is better than other categories of adherence.

Strengths and limitations

This study has several strengths. It is, to my knowledge, the first study in which the effects of different timings of adherence to COPD exacerbation action plans on health outcomes such as duration of exacerbations are studied. While the study by Farias et al.[13] studied the effect of different actions, such as taking medication or seeking help from a professional, on the duration of COPD exacerbations, adherence to the instructions to take prednisolone was only defined as either adherent (starting a course within 72 hours) or non-adherent. Studying different types of adherence

to the instruction of taking prednisolone rather than studying adherence as binary variable allows for insight into whether or not stricter adherence is preferable over less strict adherence. The categories of adherence used in this study were taken from the aforementioned as of yet unpublished study from Schrijver et al..[18] Previous studies often used adherence as a binary variable. Thus, the definitions of the categories by Schrijver et al. have not been validated in multiple studies. However, results found on COPD exacerbation characteristics in this study do match results found by Bischoff et al.[3] and Farias et al.[13] suggesting that the division between "suboptimal treatment" and "significant delay or no treatment" is one that helps differentiating the consequences of different categories of adherence. Also, the significantly different outcomes of the "treatment outside actual exacerbation period" category on COPD exacerbation characteristics and on CRQ dyspnoea in comparison with the other categories of adherence suggests that giving this form of behaviour a separate category allows for a useful differentiation in the effects of different categories of adherence on health outcomes.

A second major strength of this study is that patients with comorbidities were included. As discussed in the introduction, comorbidities are common amongst COPD patients and might influence patient's self-management, as symptom overlap between COPD exacerbations and comorbidities might cause confusion. While patients with comorbidities were not excluded in the study by Bischoff et al.[3], the percentage of patients with at least one comorbidity in this current study is higher and closer to what is described in literature on the COPD population. [5] This improves the generalizability of the results found in this study, as the patients in this study were more similar to the actual population of COPD patients.

This study also has several limitations. Since the study was retrospective, data collection was limited to data which had already been collected in the previous studies. This meant that some variables that might have helped to explain findings could not be analysed. For instance, patients' tolerance for exercise was not included, even though this is considered an important indicator of a patients' health status.[1] Exercise tolerance was not included as it was measured differently in the COPE-II study (incremental shuttle walk test (ISWT) and the COPE-III study (six-minute walking distance test (6MWT)). [7,12] While these are both valid measures for exercise tolerance in COPD-patients, there are some differences in the way these tests are performed. The 6MWT for instance is more susceptible to the influence of encouragement, which is standardized in the ISWT. [34] It was considered to transform this variable into a variable describing patients' ability to meet the respective reference value for their test, but as reference equations for the ISWT have not been described in abundance [35] it was decided not to do this. Also, one could comment that the baseline characteristic 'diabetes mellitus' should have been treated as a possible confounder. Baseline variables were treated as possible confounders when they differed significantly at $p<0.10$. The p-value for difference in diabetes was 0.10. It was chosen not to consider diabetes a possible confounder as data on diabetes mellitus diagnosis was only known for the patients from the COPE-III study. Therefore, using data on diabetes in a model might not have been reliable. It was assessed as a baseline variable as it could help indicate if the patients from the COPE-III study were evenly divided among the four categories, and it helped calculate the minimum percentage of patients in this current study with at least one comorbidity.

Lastly, another limitation was the relatively low number of patients which could be included. Only 17 patients could be included in the "suboptimal treatment" category of adherence. This limits the precision of the results found. Another consequence of the relatively low number of patients included in this study is that it is more difficult to determine statistically significant results in outcomes which have a low incidence. A difference in mortality for instance would have been

difficult to find, as both the number of patients in the study as the incidence of mortality in this study is low.

Implications for future research

As the "significant delay or no treatment" category is quite broadly defined, it cannot be said for certain that starting a course of oral prednisolone four days after the start of a COPD exacerbation is associated with poorer health outcomes as well, or if the difference found in this study was caused by patients not starting treatment at all. A larger study population, which allows for the splitting up of the "significant delay or no treatment" category into a "significant delay" category and a "no treatment" category might provide more insight into the influence of timing on the benefits of adherence to COPD exacerbation action plans.

Also, in all analyses done in this study, the "suboptimal treatment" and the "optimal treatment" category were analysed separately. Given the relatively low number of patients in the "suboptimal treatment" category it might be useful to combine both categories into one category of "adherent" patients in order to study the effect on, for instance, HRQoL. However, this is the first study to use these categories of adherence to study the effect of different categories of adherence to COPD exacerbation action plans on health outcomes. Therefore, when a larger study sample is possible, it might be wise to first study whether the "suboptimal treatment" and the "optimal treatment" categories are still similar in a larger population.

Furthermore, it might be interesting to determine whether a patients' behaviour with regard to adherence is set in stone, or whether it changes over time. Studying this change and the factors that contribute to it might help in finding ways to improve patients' adherence and help them to obtain the benefits associated with adherence.

Also, more research on the connection between category of adherence and CRQ-dyspnoea might be useful. A prospective cohort study in which the effects of different categories of adherence to COPD exacerbation action plans are studied, perhaps using a model in which both categories of adherence and COPD exacerbation characteristics are included, could be performed. This might shed some light on whether there indeed is a correlation and if so, which mechanism can be used to explain that correlation. A prospective cohort study would be able to see a correlation without the confounding of having data stem from different source studies, as the study patients were originally enrolled in was a significant yet unexplained confounder in this study.

Implications for clinical practice

As this study suggests adherence to a COPD exacerbation action plan within two days prior to or after the start of a COPD exacerbation might contribute to shorter COPD exacerbation duration, clinicians should keep in mind that adherence to the COPD exacerbation action plans might be an important part of self-management in order to improve health outcomes. Patients might gain an improvement if they were able to transfer from "significant delay or no treatment" to "suboptimal treatment" or "optimal treatment". Adherence is influenced by many factors, such as patients' health, health literacy and beliefs. [15,36–38] Thus, clinicians will have to look at each patient individually to determine how adherence can be improved. While the "treatment outside actual exacerbation period" category scored similar to the other categories, or better than the other categories of adherence, it may not be advisory for patients to change their behaviour to treating outside the actual exacerbation period.

Conclusion

The aim of this study was to determine the effect of different predetermined categories of timing of adherence to COPD exacerbation action plans in patients who experienced COPD exacerbations or took a course of oral prednisolone while having been assigned to use COPD exacerbation action plans in the COPE-II and COPE-III studies.

Timing adherence does influence some health outcomes. Adherence to a COPD exacerbation action plan by starting a course of oral prednisolone within two days prior to or after the start of a COPD exacerbation contributes to a shorter duration of COPD exacerbations, and a lower number of COPD exacerbation days per year than adherence after three days or not being adherent at all. This study provides new motivation for the studying of COPD exacerbation action plans as a helpful intervention in treating patients with COPD. No negative effects for treating outside the actual exacerbation period were observed.

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Appendices

In these appendices, some of the decisions that have been made in the making of this research proposal are explained in a more detailed manner.

Motivation of research question

The relevance of the research question has been motivated in the introduction. In determining the elements of the PICO-format, the decision has been made to call 'different levels of adherence' both intervention and comparison, as all four levels will be compared against each other. There is no clear intervention or comparison.

Motivation of chosen design

For this study, a retrospective cohort design was chosen. In this study it is aimed to answer the question *"What is the effect of different levels of adherence to COPD exacerbation action plans, by patients from the action plan group of two COPD self-management trials who experienced exacerbations and/or started prednisolone, on various health outcomes?"* This is a therapeutic question, aimed at determining the effects of a therapy. Ideally, one would study a therapeutic question via a Randomized Controlled Trial (RCT). [39] However, an RCT on this subject would take a lot of time. As COPE-II and COPE-III show, even in a one year follow-up not every selected participant has an exacerbation.[7,12] As these exacerbations are required in order for patients to have a chance to be adherent, and to benefit from an action plan, follow-up would have to be at least a year if not more. This would cost a lot of money, and more pressing for this study: time. This research was limited to twenty weeks. This would simply not have been enough time to collect patients, randomize them, allow time for follow-up and collect, analyse and discuss results. Thus, a cohort study is the next best. [40]

One could also argue that this study is a pooled analysis of two RCT's. I disagree, as, while the patients do come from two self-management RCTs, all patients come from the self-management intervention groups of those trials. These results will be pooled. The independent variable in this study, the level of adherence, has not been determined using randomization, but trough the natural course of some people being adherent earlier than others. These differences in adherence could be due to a number of reasons. Increasing age, smoking and depressed mood for instance are considered predictors for low adherence to COPD medication. [41]

Calling this study a pooled analysis of two RCT's would, in my view, claim a higher level of evidence than is actually achieved, because, as with any cohort study, confounders are a very real possibility.

The study is a *retrospective* cohort study. While one could argue that as some of the data used was collected prospectively, it is still a retrospective study.[7,12] The sub study has started after both of the studies providing the source material had ended. Also, the data on exposure i.e. adherence was collected retrospectively in both of these studies. This, again, is mostly time related. A prospective study would require the same follow-up as an RCT and would thus bring about the same problems.

Retrospective cohort studies do have some disadvantages.[39] For instance, one is limited in his choice of data and variables by what has already been documented. However, the source studies for this sub study provide for a large number of participants detailed information on exacerbations. This allows for a useful study to be conducted with limited strain on time, budget and patients. After all, no patients are required to put in any time or risk, or give up any autonomy in order for this study to be conducted.

Motivation of chosen sample

One could argue that a sample in which more, or even all, of patients had both COPD and comorbidities would provide for more detailed information on the effects of adherence to action plans in the population of COPD patients with comorbidities, which makes up approximately two thirds of the COPD patient population.[5] This might reduce the risk of sample bias.[39] Hence, analysing the effects of adherence in just the COPE-III study might seem more prudent. However, this would allow for inclusion of few patients. Dividing these patients over the four categories of adherence would bring about groups per category that are too small for meaningful analysis. Combining the data from patients who had COPD exacerbation action plans from both the COPE-II and COPE-III study could allow for inclusion of 145 patients.

Motivation of chosen definition of exposure

Most studies, in which the effect of adherence is studied, only study the difference between absolute adherence an no adherence.[3,13] In the one study that considered adherence to be a continuous variable, duration of exacerbations was not analysed.[14] Thus it cannot be concluded whether complete adherence is indeed better than sub optimal adherence. Secondly, due to the nature of the data collected on adherence in the source studies, adherence cannot be assessed as a continuous variable in this study. Using the definitions used by Schrijver et al. allows for this study to be compatible with the study by Schrijver et al.

As outcome events and adherence were measured equally in both the COPE-II and COPE-III study, the risk of measurement bias is deemed low. [39]

Motivation of chosen variables

Motivation of chosen baseline characteristics

Age

In a British study in 2012 it was found that advancing age both influences COPD severity, knowledge on COPD and the care patients receive. [42] Older patients were also at a higher risk of hospitalisation. Thus, age might have been a possible confounder, influencing both a participant's self-management abilities and their health outcomes. This might complicate findings in this study. Because of this, the categories of patients have been examined regarding the average age.

Gender

Gender in COPD is often researched. In a 2017 review on the ways in which gender influences COPD women were for instance found to have a higher susceptibility to COPD from smoking, and were more likely to have worse outcomes in HRQoL, even when the severity of their disease was the same as men.[43] Thus gender might influence the outcomes found in this study, and it is of importance that gender is distributed equally among the categories of adherence.

Smoking status

Smoking is the most important risk factor for COPD and is also associated with many of COPD's most prominent comorbidities, among which anxiety and depression.[44]

Forced Expiratory Volume $(FEV)_1$ % predicted

FEV_1 describes the volume one can force out of their lungs exhaling for one second.[7] FEV_1% predicted is the calculation of the ratio (in percentage) of the actual measured FEV_1 compared to the predicted FEV_1 for this patient. [45]The FEV_1% is a measure for the obstruction of airways. The lower the score, the more obstructed the airway. Comparing FEV_1% predicted is an important step in

determining whether disease severity is equally distributed among the four categories. If there were a significant difference in FEV_1% predicted the results will be compromised, as one cannot say whether any differences in health outcomes can be attributed to differences in adherence, or should be attributed to differences in disease severity.

GOLD-status

GOLD-status is a classification of airflow limitation in COPD patients, used as a measure of the severity of COPD. GOLD stages can be one up to and including four. While the link between GOLD-stage and health status is low,[46] and the system is recommended less now, [6] it is still an indicator of patients' health status, and has thus been compared to determine the comparability of the categories of adherence at baseline. [46]

Dyspnoea as determined by the modified medical research council (mMRC).

The mMRC is a questionnaire which measures the perceived dyspnoea in patients.[25] Patients report in it whether they experience respiratory problems in different levels of activity i.e. during rest or strenuous activity. As dyspnoea is an important symptom of COPD exacerbation, it is important to know whether there is a significant ($P<0.05$) difference in mMRC score between the different categories.[47]

Percentage of people with comorbidities per comorbidity.

The comorbidities studied each have their own pathway of influencing outcomes.[16] Therefore it is important to know whether one comorbidity is significantly overrepresented in one or more of the adherence categories. The difference could influence the results found.

Percentage of people who are employed and education level.

Looking at the percentage of people with jobs and patients' education level is used as an indicator for socioeconomic status in this study.

Percentage of people who live together.

Living together is used as an indicator for social support in this study. Social support might influence might influence health outcomes. [47]

Motivation of primary outcome

COPD exacerbations characteristics.

The COPD exacerbation characteristics that have been studied are the number of COPD exacerbations, the number of COPD exacerbation days and the duration of COPD exacerbations. Adherence to COPD exacerbation action plans is only possible when a COPD exacerbation takes place. Thus, one would not expect a difference in number of exacerbations. This outcome was thus partly used as a control, to see if separate analyses were necessary. Longer exacerbations are associated with worse health status. [4] Exacerbation free time might be associated with HRQoL. [33] Thus it is relevant to look at the duration of exacerbations.

Motivation of secondary outcomes

Health Related Quality of Life HRQoL.

HRQoL was studied as while in the Cochrane review a positive effect of the use of COPD exacerbation action plans on HRQoL was found, this was the case in neither the COPE-II nor the COPE-III study.

[7,10,12] Also, none of the studies studying the effect of adherence to COPD exacerbation action plans on health outcomes studied HRQoL as an outcome. [3,13,14] Thus, there is no solid evidence yet as to whether adherence to COPD exacerbation action plans influences HRQoL, but it is relevant to study it, as it might help understand why the evidence on COPD exacerbation action plans and HRQoL is not unanimous.

Anxiety and depression.

As explained in the introduction, there is a study in which it is suggested that adherence to a COPD exacerbation action plan has a positive effect on patients with symptoms of anxiety and depression. Thus, it is relevant to determine whether this is the case in the population of this study as well. Both the study mentioned in the introduction and the COPE-II and COPE- III studies have measured the outcome of anxiety and depression using the HADS-score.[7,12,14]

The other secondary outcomes are motivated in the research proposal itself.

Motivation of statistical analysis

Most variables did not follow normal distribution. This was expected, based on the fact that while most variables take on a normal distribution eventually, a large sample size is necessary for this to happen.[24] Often at least a hundred measurements need to be available. This is not possible in this study. Hence, non-normal distributions are not a surprise.

As explained in the text, in case of a non-normally distributed continuous outcome, such as duration of exacerbations, Kruskal Wallis ANOVA was used. This is a ANOVA analysis that uses rank numbers rather than actual values, and is thus less bothered by a non-normal distribution.[24] As Kruskal Wallis ANOVA only determines whether there is a significant difference between all four groups, when such a difference was found Mann Whitney U tests were used to determine which groups differ. However, in post-hoc tests a correction for multiple testing is necessary, to avoid overestimation of the significance of the results.[24] The Holm-Bonferroni adjusted alfas were used. These are less conservative than the Bonferroni correction, but are still doable in calculating by hand. [28,29]

In order to correct for confounding and determine the size of an effect found, linear regression was used. This method of analysis creates a prediction model for the outcome assessed following the y=ax+b structure, taking into account the effects of the input variables. Thus, the size of the effect after confounding could be determined. For each model presented in this report the R-squared value is reported. The R-squared value is a percentage which shows the amount of variance in outcome data that can be explained using this model. [24]