Chronic obstructive pulmonary disease : new insights in morning symptons and physical activity

Buul, A.R. van

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Amanda van Buul

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Prof. dr. C. Taube

CO-PROMOTOR:

Dr. M.J. Kasteleyn

LEDEN PROMOTIECOMMISSIE:

Prof. Dr. A.W.M. Evers
Prof. Dr. M.A. Spruit (Maastricht University, Maastricht)
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"Niet omdat het moet, maar omdat het kan"
Omdat het kan – INDIE-Amsterdam, 2015

CONTENTS

Introduction

GENERAL INTRODUCTION OF COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that is characterised by airway obstruction and chronic inflammation of the airways. According to the latest information of the World Health Organisation (WHO), COPD is the third leading cause of death worldwide.[1] The most common symptoms in COPD are dyspnoea, chronic cough and sputum production. Components of COPD such as emphysema and chronic bronchitis were first described in 17th century.[2] In the 19th century, hyperinflated lungs were discovered in particular families, indicating that there should be familial predispositions or environmental factors that cause long abnormalities. Nowadays, the most important causes of COPD are exposition to noxious gases and tobacco smoking. A diagnosis of COPD should be considered in any patient with symptoms of dyspnoea, chronic cough or sputum production and a history of risk factors for COPD.[3]

Diagnosis

If there is a suspicion of COPD, the diagnosis should be confirmed by pulmonary function testing. Typical for COPD is airway obstruction that is caused by narrowing of the small airways, alveolar damage and loss of elasticity of the lungs.[4] Airway obstruction is defined as a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) lower than 0.7 or FEV_1/FVC below the lower limit of normal (LLN). The severity of airflow limitation is expressed as a percentage of predicted FEV_1. There are four COPD stages: mild (FEV_1 ≥80% predicted), moderate (50% ≤ FEV_1 <80% predicted), severe (30% ≤ FEV_1 <50% predicted) and very severe COPD (FEV_1 <30% predicted).[3] Airflow limitation solely is not enough to stage COPD severity. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) statement, patients' symptoms, history of exacerbations and thereby risk of future exacerbations should be taken into account as well.[3] Higher symptom burden[5] and a higher number of severe exacerbations are related with higher mortality rates.[6, 7]

Treatment

There are no curative options for COPD. Major treatment goals in COPD are reduction of symptoms and prevention of acute exacerbations. Symptoms can be monitored with questionnaires. The most widely used questionnaires are the modified Medical Research Council (mMRC),[8] COPD Assessment Test (CAT)[9] and Clinical COPD Questionnaire (CCQ).[10] For the risk assessment for future exacerbations, the number of moderate and severe exacerbations should be used as a predictor, since previous exacerbations are the best predictor for future exacerbations.[11] An exacerbation is defined as a sudden worsening of respiratory symptoms that results in additional therapy.[3] A low risk for

future exacerbations is defined as having had 0 or 1 exacerbation during the previous year (not leading to hospital admission); high risk as ≥2 exacerbations or ≥1 leading to hospital admission. Pharmacological and non-pharmacological treatment are developed to reduce symptoms and prevent exacerbations. Most prescribed pharmacological treatment are bronchodilators and inhaled corticosteroids. However, pharmacological treatment has no effect on mortality.[3] Moreover, non-pharmacological interventions are recommended to improve COPD status. These interventions include the reduction of exposure to risk factors and smoking cessation, education and self-management, adequate sleep, a healthy diet, exercise training and sufficient physical activity. Despite the existing treatment options, COPD is still in the top five leading causes of disability-adjusted life-years.[12] Therefore, more research is needed in factors that are related with poor outcomes in COPD to encourage the development of novel treatment options. In this thesis the focus is on morning symptoms and physical activity.

MORNING SYMPTOMS IN COPD

Occurrence

In COPD, symptoms vary over the day.[13] However, for decades, morning symptoms were considered a feature of asthma.[14] In 2009, the first study with focus on morning symptoms in COPD was published.[15] This study showed that the majority of patients with COPD experience morning symptoms. Following this study, more research has been conducted in this field. Depending on the used questionnaire and the study population, 39.8 to 94.4% of all COPD patients experience symptoms in the morning.[15-22] Most frequently occurring morning symptoms are coughing, sputum production and shortness of breath. Morning symptoms are in general mild to moderate.[16, 19, 22] Patients mentioned morning symptoms as a cause of work absenteeism.[23]

Assessment

Nine years after the first publication about morning symptoms in COPD, a morning symptoms questionnaire was validated.[24] Before that, researchers used non-validated morning symptom questionnaires.[18, 25-30] These different questionnaires contained one to nineteen questions about morning symptoms and most of them evaluated the type of symptoms, severity of symptoms and the impact of the symptoms on daily life. Furthermore, some studies used non-COPD specific questionnaires that included one or more questions about morning symptoms.[18, 25, 31-33]

Associated factors

It has been shown that morning symptoms are associated with night time symptoms, [19, 21, 22] poorer health status,[19, 21, 22, 33, 34] current smoking, exacerbations,[19, 21, 22] more depression,[19] more anxiety,[19] more use of oxygen in the previous week,[22] more use of rescue medication and more primary care visits. It is unknown whether morning symptoms could be a target for therapy to improve these outcomes since the causality between morning symptoms and other factors is still unknown.

PHYSICAL ACTIVITY IN GENERAL

Definition and recommendations

Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure."[35] As this definition already suggests, movements vary in intensity. The intensity of physical activity can be expressed in metabolic equivalents (METs). One MET is nearly equivalent to the energy expenditure of sitting quietly.[36] Activities that cost <3.0 MET are categorised as light intense activities, for example hair styling. Activities that cost 3.0 to 6.0 MET are categorised as moderate intense activities, for example walking the dog. Activities that cost >6.0 MET are categorised as (very) vigorous intense activities, for example jogging.[36] According to the physical activity recommendations of American College of Sports and Medicine, adults should be physically active for at least 30 minutes a day in moderate intense physical activity in bouts of at least 10 minutes, for at least five days a week.[37] Another option to reach the activity recommendations is to be physically active 20 minutes a day in vigorous intense physical activity in bouts of at least 10 minutes, for at least three days a week. When physical activity recommendations are not reached, a person is physically inactive. Older adults are less likely to reach the activity recommendations than younger adults.[38] The physical activity domains in which people spent their time have changed during the past decades; less time is spent in work and transport-related physical activity due to the development of new technologies and urbanisation; and more time could be spent in leisure time physical activity. Changing physical activity is challenging, because physical inactivity is associated with several factors including low interest in physical activity, low education level, health related factors and a high body mass index.[39, 40]

Measurements

There are various methods to assess physical activity. One method to assess physical activity is the use of activity questionnaires. Activity questionnaires are easy to use in practice and they are cheap.[41] Disadvantages are recall bias and (gross) overestimation of physical activity.[41] Objective assessments of physical activity can be performed with devices.

Pedometers are most accurate in step counting.[42] However, pedometers do not contain information about movement intensity. (Triaxial) accelerometers are devices that assess acceleration in multiple directions and thereby reflect bodily movement. Several accelerometers have been developed, with different features, designs and measured output.[43, 44] Disadvantages of accelerometry are lack of adherence and the need for technical expertise.[41] In COPD, accelerometers are validated tools to evaluate physical activity.[44]

Chronic diseases

Physical inactivity results in a higher risk of cardiovascular disease, various types of cancer, diabetes, obesity and mortality. [45-48] Physical inactivity is common in chronic diseases such as COPD, cardiovascular diseases, kidney disease and diabetes.[49] In a group of adults without a chronic disease about 50% is physically active, whereas only 30% of patients with a history of COPD reach the recommended physical activity levels.[49]

PHYSICAL ACTIVITY IN COPD

Known activity characteristics

Physical activity is substantially lower in patients with COPD than their healthy peers.[50, 51] Physical inactivity is not specific to severe COPD only; the decline is already present in mild and moderate COPD[52] and pulmonary function is only weakly associated with physical activity.[53] There is an annual decrease in physical activity.[54] Low physical activity in COPD is related to high mortality rates,[55] lower quality of life, more dyspnoea and more previous exacerbations.[56] Thus, physical inactivity seems to be a matter of concern in COPD that needs to be addressed. It is unknown whether COPD causes inactivity due to symptoms, or that it is actually the other way around: that physical activity is a risk factor for the development of COPD symptoms. Previous research has shown that patients with COPD have different activity characteristics when compared to their healthy peers: patients with COPD perform activities slower,[15] at a lower walking speed,[46] and there is an increased duration between steps.[57] Furthermore, they take more breaks[15] and they perform activities in fewer and shorter bouts.[53]

Decrease in physical activity

Patients with COPD experience barriers to be physically active, such as a lack of infrastructure, lack of willpower, other psychological problems, lack of time, invalidating symptoms like dyspnoea and fatigue.[58, 59] Moderate and severe acute exacerbations of COPD drastically decrease physical activity.[60] Frequently, these exacerbations lead to hospitalizations. Following hospitalization, it is difficult for patients to perform physical activities.

It generally takes more than one month to become as active as they were before the exacerbation, if they even return to their pre-exacerbation level.[61]

Physical activity stimulation

Regular physical activity is recommended for all COPD patients.[3] Some level of physical activity results in less decline in pulmonary function when compared to patients who live a sedentary lifestyle.[54] Therefore, (easy) interventions to improve physical activity should be developed. Several interventions are proven to be effective: counselling, direct physical activity feedback and pulmonary medication. Physical activity counseling and real-time feedback were more successful in studies that included stable patients with COPD[62, 63] than studies that included unstable patients. Placebo-controlled medication trials have shown positive effects of long-acting beta2 agonists (LABA)[64, 65] and a long-acting muscarinic antagonist (LAMA)/LABA combination on physical activity parameters.[66] Pulmonary rehabilitation is a multidisciplinary intervention with focus on exercise training, education and behaviour change to improve physical and psychological conditions.[67] The effects of pulmonary rehabilitation are inconsistent; some studies have shown no significant effects on physical activity[68, 69], while others shown significant improvements.[70, 71] Maintenance of the positive effects of pulmonary rehabilitation on the longer term is challenging.[72]

OUTLINE OF THE THESIS

There are no curative options for COPD yet. Nowadays, COPD is still in the top five of diseases that are responsible for disability-adjusted life-years worldwide.[12] Therefore, more research is needed to improve factors that are related with poor outcomes in COPD. The aim of this thesis was to gain more knowledge about morning symptoms and physical activity in COPD in search of novel treatment options. In the studies described in this thesis, morning symptoms were assessed with a questionnaire and physical activity was assessed with a physical activity questionnaire and/or accelerometry.

Chapter 2 is a systematic review on the existing evidence about the association between morning symptoms and physical activity in COPD. Following this systematic review, the MOrning symptoms in-Depth observationAl Study (MODAS) was conducted to investigate the association between morning symptoms and objectively measured physical activity. The results of this study are described in **chapter 3** and **chapter 4.**

In the MODAS, the focus was on moderate to very severe COPD patients. However, physical inactivity is already present in mild and moderate COPD. Therefore, physical activity was

studied in non-severe COPD patients as well. We studied the associations between physical activity and other patient characteristics. The results are presented in **chapter 5**.

This thesis continues with an evaluation of a novel systematic approach for asthma and COPD patients referred to secondary care pulmonology. The novel systematic approach consisted of a predefined diagnostic evaluation combined with an optional internet-based self-management support system. Outcomes of the systematic approach were compared with usual care. The results are shown in **chapter 6**. Finally, in **chapter 7**, a summary of the most important findings, a discussion and suggestions for further research and clinical practice is presented.

LIST OF ABBREVIATIONS

CAT: COPD Assessment Test
CCQ: Clinical COPD Questionnaire
COPD: chronic obstructive pulmonary disease
FEV_1: forced expiratory volume in one second
FVC: forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
LABA: Long-acting beta2 agonist
LABA: Long-acting muscarinic antagonist
LLN: lower limit of normal
METs: metabolic equivalents
mMRC: Medical Research Council
MODAS: MOrning symptoms in-Depth observationAl Study
WHO: World Health Organisation

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Association between morning symptoms and physical activity in COPD: a systematic review

Authors

Amanda R. van Buul[1]
Marise J. Kasteleyn[1]
Niels H. Chavannes[2]
Christian Taube[1]

Affiliations

[1]Dept of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands.
[2]Dept of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands.

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ABSTRACT

Morning symptoms are common in chronic obstructive pulmonary disease (COPD). Many COPD patients consider the morning as the most troublesome part of the day, in which they experience more symptoms and physical activity limitations.

To systematically report evidence of the association between morning symptoms and physical activity in COPD patients, a literature search was conducted using relevant MESH terms and text words in PubMed, Embase, Web of Science, COCHRANE, CINAHL and PsycINFO. Quality of the articles was assessed with validated checklists.

Eight studies were included. Morning symptoms were present in 39.8-94.4%. In 37.0-90.6% of all COPD patients, there was an association between physical activity and morning symptoms. However, causality could not be proved. Morning symptoms were associated with a sedentary lifestyle ($p<0.05$). Treatment in line with the guidelines improved the degree of activity limitations due to morning symptoms ($p<0.0001$).

Across all disease stages, COPD patients experience morning symptoms which are negatively associated with physical activity. Physicians should consider morning symptoms as a treatment goal. Pharmacotherapy may improve the degree of activity limitations due to morning symptoms. More objective research should focus on symptoms, activity limitations and physical inactivity of COPD patients, especially in the morning.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has a huge socio-economic impact. COPD is the fourth cause of years of life lost according to the latest findings of the Global Burden of Disease Study [1] whereas the World Health Organization stated COPD as the third leading cause of death in the period 2000-2012 [2]. COPD is not a curable disease; therefore, the main focus of pharmacotherapy is to limit or reduce symptoms as much as possible and to prevent acute exacerbations. In addition, reduction of mortality is an important treatment goal. However, so far, no pharmacological intervention has been able to reduce mortality in COPD patients [3]. The actual consensus report of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend non-pharmacological interventions such as smoking cessation, avoiding exposure to air pollution and increased physical activity as well as pharmacological treatment and adequate use of medication [4]. In current guidelines, severity of disease is categorised by lung function as well as symptoms and the occurrence of acute exacerbations. Symptoms have especially been found to have an important impact in overall health status [5] and are therefore of importance from the patient's perspective. In addition, there is a strong association between increased shortness of breath and difficulty with physical activities [6;7]. Frequently, symptoms occur in the morning, resulting in limitations of morning activities and often in work absenteeism as well [8]. Despite the large impact of morning symptoms on activities and quality of life, morning symptoms are not a focus of current treatment guidelines and have not been mentioned in the official European Respiratory Society statement on physical activity in COPD [3]. Still, there is growing awareness of the impact of COPD symptoms in the morning and an increasing number of tools to evaluate morning symptoms have been developed [8]. To further investigate the impact of morning symptoms on patients with COPD and especially on physical activity, we performed a structural literature review of the current knowledge of the association between morning symptoms and physical activity in patients with COPD.

MATERIALS AND METHODS

Data sources and searches

An electronic search of the literature was performed on October 27, 2015, using relevant MESH terms and text words. The search was performed using PubMed, Embase, Web of Science, COCHRANE, CINAHL and PsycINFO. There was no limitation for date of publication. All types of studies were included, except meeting abstracts, reviews and articles from non-peer-reviewed journals. Original complete texts in all languages were used and the actual studies may have been conducted in any country. The full search is available in the supplementary material.

Study selection

Two authors (AvB and MK) screened the titles to include the relevant articles. Studies were included if the study population consisted of patients with the diagnosis COPD. Studies were excluded when the predefined outcomes did not comprise either morning symptoms or physical activity. After this first screening, two authors (AvB and MK) screened the abstracts to only include relevant articles (figure 1). Abstracts that did not include both morning symptoms and physical activity were excluded. If an abstract suggested that a substantial part of the article concerned morning symptoms and physical activity, it was included. A third author (NC) reviewed abstracts when there was a disagreement between AvB and MK. Of the remaining articles, AvB and MK read the full-texts. The same inclusion and exclusion criteria as for the abstracts were used for the full-texts.

Synthesis and report strategy

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [9] was used to give insight into the amount of excluded articles. To review the current knowledge of morning symptoms and physical activity in COPD patients, the occurrence of morning symptoms, the association of morning symptoms with physical activity limitations and the impact of medication on activity limitations associated with morning symptoms were evaluated. The occurrence of morning symptoms was studied in three ways. First, the incidence of morning symptoms in COPD was examined to determine the frequency of these symptoms. The occurrence of morning symptoms in all COPD patients and the type of morning symptoms was assessed in studies in which all COPD patients were included regardless whether they experienced symptoms or not. Second, in studies with patients with morning symptoms, the type of morning symptoms were examined to determine the most common. Third, in studies with patients with symptoms during any part of the day, the percentage of patients that reported morning as the worst time of the day was determined. Furthermore, the association between morning symptoms and physical activity was assessed. Thereafter, the impact of medication on physical activity limitations that were associated with morning symptoms was evaluated. No further statistical analysis or meta-analysis has been conducted, as all studies had different endpoints and the endpoints were measured with different tools.

Quality assessment

The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist [10] was used to assess the quality of observational, case control and cohort studies. The Consolidated Standards of Reporting Trials (CONSORT) checklist [11] was used for the quality assessment of randomized controlled trials. There is no consensus when an article may be indicated as high or low; however, previous research has shown that observational studies published in high-quality journals contain an average of 69% of the STROBE items

[12]. Consistent with this study and other studies who support this interpretation [13;14], a minimum of 15 (69%) reported items out of 22 indicated "high quality", and lower than 15 out of 22 indicated "moderate to low quality".

RESULTS

Search strategy

The search identified 390 articles. After removing duplicates, 195 individual articles remained. After screening titles, 117 articles were considered relevant. After reading abstracts, 32 articles remained. Full-texts of these articles have been read and 24 articles have been excluded. Eight remaining studies were included in this systematic review (figure 1). Of the eight included studies, seven studies were observational studies and one was a randomised controlled trial. The quality of the studies was assessed using the STROBE checklist. The scores ranged from 14 to 18 out of 22 points. This means that six observational studies had high quality and one observational study had a moderate quality. One article was a randomised controlled trial and was assessed by the CONSORT checklist. This article scored 17 out of 25 points. This is a study that pooled analysis from two studies. The full methods of the two studies are not described in the present study. When using the methods of the original studies, the study would score a higher amount of points. None of the included articles had a low quality (see supplementary table S2).

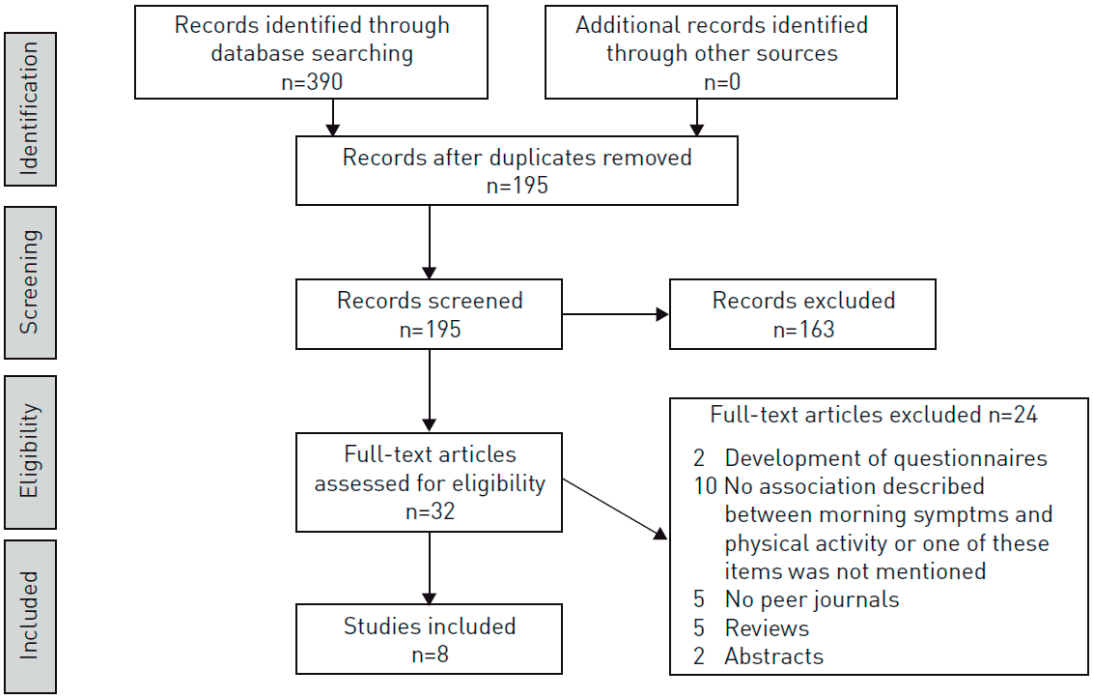

Figure 1 Study flow diagram with the use of the official PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart.

General findings

The oldest study was published in 2009 and the most recent in 2015. The number of patients included in the studies ranged from 133 to 3394. Patients participating were at least 30 years old, 5.3-60.5% were female. In all studies, at least 24% of patients were current smokers. All stages of COPD were represented. The study population and the general conclusion of each study are reported in table 1.

Morning symptoms

When analysing all patients with COPD, the most common morning symptoms were cough, sputum production and shortness of breath [15-17]. In this patient group the percentage of morning symptoms varied between 39.8 and 94.4% [15-20] (figure 2a). When only assessing the group of patients with morning symptoms, again cough, sputum production and shortness of breath were frequently detected [19-21] (figure 2b). In symptomatic severe and very severe COPD patients, it was found that the morning was the worst time of the day for the symptom sputum production (in 70.9-87.2%), for cough (in 60.1-72.6%) and for shortness of breath (in 45.4-85.1%) [18;21;22] (Figure 2c). More than half of patients considered the severity of their symptoms to be mild to moderate [15;16;20]. The association between COPD severity and morning symptoms was analysed. Interestingly, morning symptoms could be detected across all stages of disease. One study that included COPD patients with all stages of the disease, concluded that morning symptoms were associated with the severity of COPD [16]. However, when only patients with severe and very severe COPD were included, no difference in pulmonary function between patients with or without morning symptoms could be detected [18]. Nevertheless, when patients over all disease stages were included, a significant decreased pulmonary function could be detected in patients with morning symptoms compared with those without morning symptoms [17]. Mostly, patients do not experience solely morning symptoms, but might experience daytime and night-time problems as well [16;17;20]. Most common night-time problems were night-time symptoms, sleep disturbances and early awaking [15-18;20;22].

The association between morning symptoms and physical activity

All studies showed that COPD patients who experience morning symptoms also report a negative impact on physical activity. When analysing all patients with COPD, 37-90.6% of patients experienced physical activity limitations that were associated with morning symptoms [15;18;21] (table 2). When just patients with morning symptoms were assessed, 34-79% of these patients reported limitations in morning activities due to these symptoms [19;20]. Most mentioned limited activities were getting up, taking a shower and dressing [18;19;22]. Reported routine activities took at least 10 min longer compared with the situation before morning symptoms had increased [19]. Half of patients reported to have

Table 1 Overall conclusion and quality of included studies

First author [ref.]	Study design	Participants' characteristics at baseline	Overall conclusion	Quality
Bateman [15]	Pooled analysis from two phase III double-blind, randomised, parallel-group active- and placebo-controlled studies	*n* = 3394; ≥40yr; stable moderate to severe COPD	Aclidinium/formoterol 400/12µg significantly improves 24-hour symptom control compared with placebo or aclidinium or formoterol alone. The frequency of exacerbations was also reduced compared with placebo	17/25[#,¶]
Stephenson [20]	Cross-sectional survey study	*n* = 752; 60.5% female; ≥40yr; COPD plus at least one pharmacy claim for maintenance COPD medication	The majority of the patients with night time or morning symptoms experience at least three distinct types of symptoms a week. Approximately half of them consider their symptoms to be moderate to severe. They felt that their symptoms had impact on their sleep and morning activities, and they were anxious	18/22[†]
Miravitlles [16]	Observational study	*n* = 727; 34.2% female; ≥40yr; current of former smokers; stable mild to very severe COPD	More than half of COPD patients experience symptoms throughout the whole day. There was a significant association between night time, early morning and daytime symptoms. In each period, symptoms were associated with worse patient-reported outcomes	18/22[†]
O'Hagan [19]	Observational study	*n* = 811; 44% female; age 30-70yr; COPD diagnosed by a physician; at least one morning symptom	Morning symptoms can severely interfere with COPD patients' ability to perform tasks throughout the day. Half of the patients had made changes in their morning routines	15/22[†]
Roche [17]	Cross-sectional observational study	*n* = 1489; 34.3% female; ≥40yr; with a history of smoking, airflow obstruction and the diagnosis COPD	39.8% of the COPD patients experience morning symptoms. Morning symptoms are associated with poorer health status, impaired daily activities and increased risk of exacerbations	16/22[†]
Kim [18]	Prospective non-interventional and observational study	*n* = 133; 5.3% female; >45yr; with a history of smoking; stable severe to very severe COPD	57% of COPD patients experience limitation in their activities due to morning symptoms. These patients also have more prevalent and severe COPD symptoms	14/22[†]
Kessler [22]	Cross-sectional observational study	*n* = 2441; >45yr; 21,5% female, with a history of smoking; stable severe to very severe COPD	Patient-perceived COPD symptoms vary over the day and the week, and have impact on activities. The morning was considered the worst time of the day	16/22[†]
Partridge [21]	Quantitative internet interviews	*n* = 803; ≥40yr; 44% female; with a history of smoking; all stages of COPD	COPD are worst during the morning. Many patients consider the impact of COPD on morning activities to be extensive	17/22[†]

COPD: Chronic obstructive pulmonary disease; [#]: CONSORT (Consolidated Standards of Reporting Trials) was used as a tool to assess quality; [¶]: pooled analysis from two studies; [†]STROBE (Strengthening the Reporting of OBservational studies in Epidemiology) was used as a tool used to assess quality.

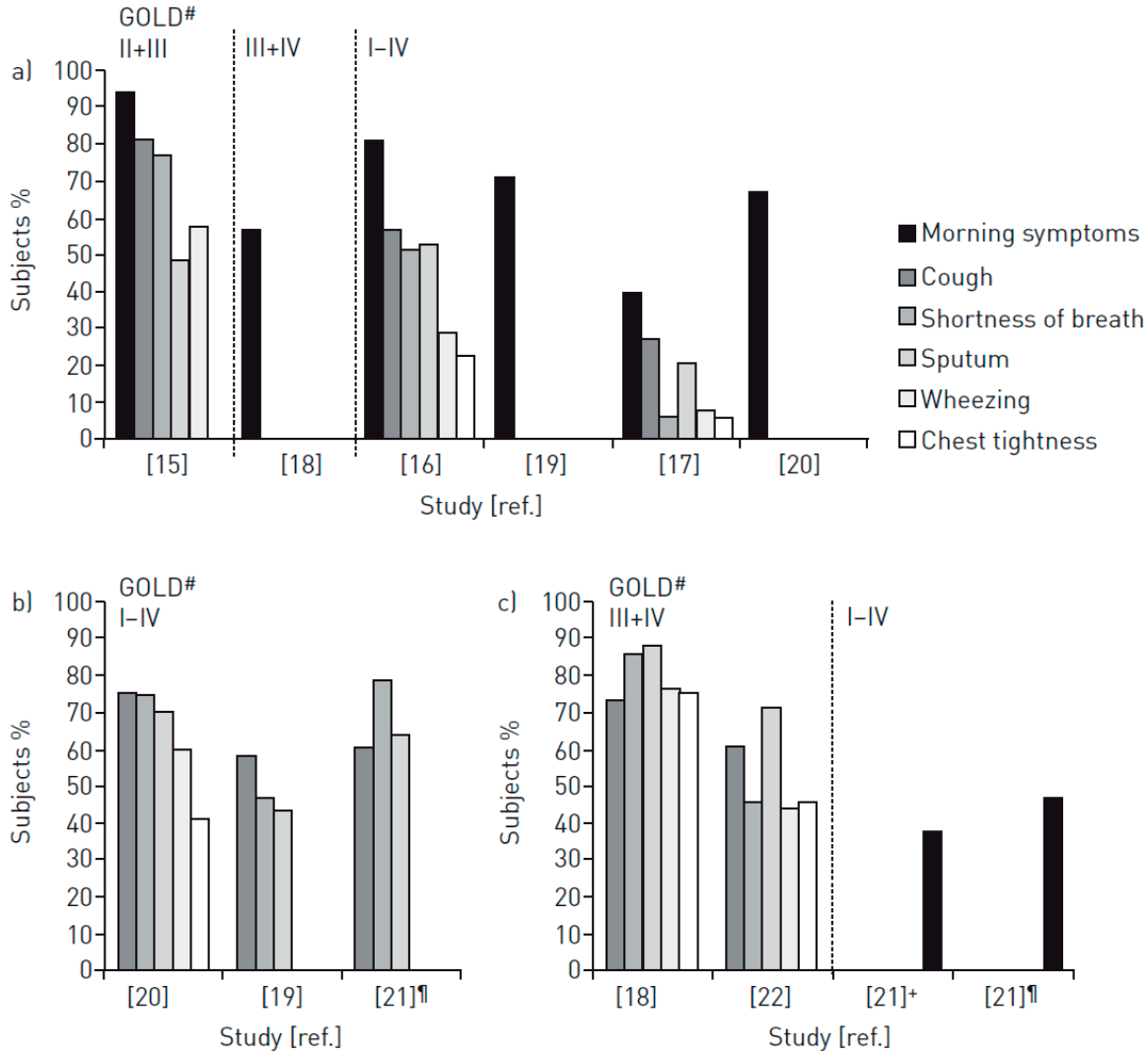

Figure 2 Occurrence of morning symptoms. a) In all studied chronic obstructive pulmonary disease (COPD) patients. b) Occurrence of different morning symptoms in COPD patients experiencing symptoms. c) Symptomatic COPD patients who report the morning as worst time of the day for that symptom (results for at waking and the rest of the morning are combined). #: Classification of airflow limitation according to Global initiative for Chronic Obstructive Lung Disease (GOLD). ¶: "Severe" was defined in this study as regular use of COPD medication plus a third level of breathlessness or above using Medical Research Council dyspnoea scale and one or more exacerbations in the preceding 12 months; +: in all included COPD patients.

made changes to their morning routines because of morning symptoms [19]. Patients' core coping strategies were doing things slowly and taking more breaks [21]. Shortness of breath was the symptom most strongly correlated with the reduced ability to perform tasks [21]. One of the studies, which included only patients with severe to very severe COPD, reported that 9.4% was completely unable to exercise outside, 24.7% managing up to 30 min·day–1, 32.9% between 30 and 60 min·day–1 and 30.9% reported walking outdoors longer than 1h·day–1 [22]. In another article, 30% of patients described themselves as sedentary, 38% as moderately active and 34% as active. There was a significant association between morning symptoms and patients' self-reported physical activity. Sedentary

Table 2 Influence of morning symptoms on physical activity

First author [ref.]	Stage of the COPD	Definition of the morning	Method to evaluate morning symptoms and activity limitations	Physical activity limitation that are associated with morning symptoms	Self-reported limitations	Conclusion
Bateman [15]	Moderate to severe	As described in the EMSCI and NiSCI	Questionnaires (EMSCI and NiSCI) for the patients	90.6% of all patients with COPD	NA	Most COPD patients with morning symptoms considered that their symptoms affect their morning activities
Stephenson [20]	All stages	Time of getting out of bed and approximately 11:00h	A 30-min questionnaire for patients about morning symptoms and the impact on morning activities	60.4%[#]	Work[§]	More than half of patients considered that their symptoms affect their morning activities
Miravitlles [16]	All stages	Time of getting out of bed and approximately 11:00h	Patients filled out a Night-time, Morning and Daytime Symptoms of COPD questionnaire, developed by the sponsor	Patients who are sedentary experience more symptoms in any part of the day (also in the morning) $p<0.05$	NA	In each part of the day (morning, daytime, night time) there was an significant association between symptoms and a low physical activity level
O'Hagan [19]	All stages	Not defined	Online questionnaire consisting predefined questions for patients	34 to 79%[#] have problems with common morning activities; 56 to 70%[#] with more physically demanding activities	Self-care, domestic activities and work[§]	Morning symptoms can severely compromise patients' ability to perform, even simple tasks. Half of the patients had made changes to their morning routines
Roche [17]	All stages	Symptoms that are present when getting up in the morning, thus those symptoms present on waking, rather than those persisting through the morning	Questionnaires with predefined questions. Physicians gave information about severity grade of the symptoms; patients about the impact on daily life	Impact on normal activities was higher in those with morning symptoms (3.96 vs. 3.29[+], $p=0.007$)	Self-care and work[§]	Impact on daily activities was significantly higher in patients with morning symptoms than without

Table 2 Influence of morning symptoms on physical activity (*continued*)

First author [ref.]	Stage of the COPD	Definition of the morning	Method to evaluate morning symptoms and activity limitations	Physical activity limitation that are associated with morning symptoms	Self-reported limitations	Conclusion
Kim [18]	Severe to very severe	Not defined	Patients filled out the CSQ. Those who reported morning symptoms, subsequently completed the MAQ	57% of all patients with COPD	Self-care and domestic activities[§]	57% of COPD patients has considerable impact on their morning activities
Kessler [22]	Severe to very severe	In the morning, after waking up and later in the morning	Interview over the telephone. Predefined questions developed by the sponsor	35.4 to 41.0% of patients that experience any symptom, felt that morning symptoms affect morning activities	Self-care[§]	There was an association between morning symptoms and the impact on activities
Partridge [21]	All stages	From the time woke up until they were dressed, had breakfast and were ready to start the day	Predefined questions were answered by the patient by an internet interview	37% of all COPD patients and 73% of the severe[¶] COPD patients regarded problems associated with morning routines as bothersome. 74% of all COPD patients and 96% of the severe[¶] patients reported that they took longer to complete their morning routines	Self-care and domestic activities[§]	Many patients considered the impact of COPD on morning activities to be extensive

COPD: chronic obstructive pulmonary disease; CSQ: clinical symptom questionnaire; EMSCI: early-morning symptoms of COPD instrument; MAQ: morning activity questionnaire; NiSCI: night-time symptoms of COPD instrument. [#]: In patients with morning symptoms; [¶]: "Severe" was defined in this study as: regular use of COPD medication plus a third level of breathlessness or above using Medical Research Council dyspnoea scale and one or more exacerbations in the preceding 12 months; [+]: Measured on a 7-point Likert scale of 0=no impact to 7=constant impact; [§]: More detailed information in Supplementary table 3.

patients experience more morning symptoms and more symptoms the rest of the day when compared with moderately active or active patients ($p<0.05$) [16], although it was not reported whether inactivity was actually a result of morning symptoms. Besides morning activities, normal daily activities are also influenced by morning symptoms [17;19;22]. More detailed information about the sort of activities is given in supplementary table 3.

Treatment to improve activity limitations that are associated with morning symptoms

An internet survey stated that about 79% of COPD patients report that medication provides relief of symptoms in the morning [19]. A prospective non-interventional observational study in which patients were treated following present guidelines with pharmacological or non-pharmacological therapies, showed that the impairment of all activities that were associated with morning symptoms was significantly reduced [18] (table 3). Recently, data from two phase III, double-blind, randomised, parallel-group active- and placebo-controlled studies were pooled to compare the effect of a fixed dose combination of long acting 2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) versus mono-therapy or placebo on morning symptoms and associated physical activity limitations [15]. In this analysis, there was a significant improvement of morning symptoms and the individual symptoms cough, wheezing, dyspnoea and sputum production in the morning after treatment with the fixed LABA/LAMA combination. In the same study, the fixed LABA/LAMA combination significantly improved severity scores for limitations of morning activities that are associated with morning symptoms when compared with LABA and LAMA alone (both $p<0.05$) (table 3). Furthermore, in an internet survey, it was found that improvement in the ability to perform morning activities is one of the patients' expectations of treatment [19]. Nevertheless, patients reported that physicians were unlikely to ask about morning symptoms and the ability to perform morning activities [19;21]. Hence, physicians were unlikely to discuss how to cope with these symptoms and to describe what to expect from therapy for activity limitations.

Table 3 Impact of medication on morning symptoms and physical activity

First author [ref.]	Medication	Morning symptoms	Physical activity limitation that are associated with morning symptoms	Effect medication on morning symptoms	Effect intervention/ medication on physical activity limitation due to morning symptoms
Bateman [15]	Aclidinium bromide/ formoterol	94.4% of all patients	90.6% of all patients	FDC 400/12ug on severity scores: -0.23 units (-17.0%); aclidinium 400ug: -0.14 units (-10.7%); formoterol 12ug: -0.17 units (-13.6%) p <0.0001 vs. aclidinium and p <0.01 vs formoterol.[#] Individual morning symptoms: p<0.05 vs. aclidinium for cough and difficulty bringing up phlegm, and vs. both monotherapies for wheezing and shortness of breath	Improvements in limitation of early morning activities: p <0.05 vs. aclidinium and p <0.05 vs. formoterol
O'Hagan [19]	Patients were allowed to select any of their applied medication	Morning symptoms was an inclusion criterion in this study	Impact on normal activities was higher in those with morning symptoms compared to those without (3.96 vs. 3.29, p<0.007)	79% of COPD patients who feel medications provides relief from symptoms in the morning enough	33% of patients considered "improvement of ability to carry out morning activities" a key treatment goal. 21% of patients feel medication provides improvement in the ability to carry out morning activities
Kim [18]	No standard treatment for COPD was defined by the study protocol	57% of all patients	57% of all patients	LAMA and ICS plus LABA were used significantly less frequent in patients with morning symptoms. LAMA was a preventive factor for the presence of morning symptoms	Severity of all morning activities were significantly reduced after two months follow-up.

COPD: chronic obstructive pulmonary disease; FDC: fixed-dose combination; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonists. [#]: Symptom severity measured on a score from 0 (no symptoms) to 4 (very severe symptoms).

DISCUSSION

The aim of the present study was to systematically review the current evidence of the association between morning symptoms and physical activity in COPD patients. The most dated study included in this review was from 2009, suggesting that interest for the combination of these topics is relatively recent. None of the studies had a low quality when scored

with the STROBE and the CONSORT tools. Therefore, all eligible articles were included in the present review. It was found that morning symptoms are common in patients with COPD across all stages. Importantly, these symptoms are associated with impaired physical activity.

Morning symptoms in COPD were detected frequently in different studies. However, the percentage of patients with symptoms varied widely. One explanation might be that different definitions for morning were used. In the studies a lower percentage of morning symptoms could reflect just the symptoms immediately on awaking and a higher percentage of morning symptoms reflects the symptoms on awaking plus the symptoms that develop throughout the rest of the morning. There are some tools developed to evaluate morning symptoms [23-25], but none of them have been adequately validated. In the included articles, mostly self-developed questionnaires were used, and only one article used one of the previously mentioned tools. In some studies, only patients with severe and very severe COPD were included; while, in other studies, mild to moderate COPD patients were also included. It is of note that morning symptoms were apparent in all stages of COPD and that activity limitations associated with morning symptoms were detected in less severe COPD. This is in line with studies showing that physical activity of patients with COPD is already impaired in early disease stages [26]. Therefore, the difference in percentage of morning symptoms cannot be explained by the different study populations of the included studies. Currently, there is lack of evidence that morning symptoms increase as the degree of severity of COPD increases. In three included studies [19-21] lung function was unknown. In one study the authors made their own definition for "severe COPD" that was not linked to pulmonary function [21]. In other studies the authors did not analyse the patients by pulmonary function [15;19;22]. One further explanation for the diverse results might be that questionnaires are not always filled out by the patients. In some studies the physician scored the severity of symptoms, which could further explain the wide range of incidences of morning symptoms. Previous research has shown that there is a low level of concordance in assessing disease impact between COPD patients and physicians [27]. Furthermore, it can also be stipulated that differences in methods of data collection (electronically or by paper) could affect the results. However, we believe that the impact of different data collection methods is minimal, since data administered on paper are quantitatively comparable with measures administered on an electronic device [28;29]. There are some disorders and conditions that may affect symptoms in the morning as well. Mostly, patients do not experience only morning symptoms, but experience daytime and night-time symptoms as well. Symptoms during daytime or night-time negatively influence health status, anxiety and depression levels, sleep quality, physical activity levels and adherence to medication. Patients with morning symptoms were more likely to use oxygen in the previous week [20], to have poorer health status [16;17;20], to experience exacerba-

tions [16;17;20], have a worse sleep quality [16] and have higher anxiety and depression levels [16]. It is not possible yet to distinguish whether morning symptoms are a particular phenotype in COPD or whether it is a feature of the disease.

A large group of COPD patients have physical activity limitations that are associated with morning symptoms. This raises the question whether people with morning symptoms are more inactive, or inactive patients have more morning symptoms. Until now, prospective comparative studies using objective measures of physical activity levels in relation to morning symptoms are lacking. Existing evidence about physical activity and morning symptoms mostly comes from observational studies. Thus, causality between morning symptoms and limitations of activities cannot be proven. It is has been shown that people with COPD are more physically inactive compared with their healthy peers [30;31]. However, it is not completely clear if the relationship between the level of inactivity is solely a result of COPD or if inactivity is a risk factor and contributes to the development of COPD itself. Indeed, patients report frequently that dyspnoea impairs everyday tasks [32]. Especially in the morning while performing tasks, patients' main coping strategies are doing things slowly and taking frequent breaks [21]. This is in line with previous research demonstrating a low walking speed is typical for COPD patients compared with healthy controls [3]. Therefore, it has been suggested that patients with COPD may be in a downward spiral of symptom-induced inactivity, as well as in the early stages of disease [30;31]. However, impaired physical inactivity is not an exclusive feature of patients with COPD but has been reported in many different chronic diseases such as stroke, kidney disease, diabetes, coronary heart disease, hypertension and obesity [33]. This suggests that also other factors such as behavioural, genetic, social, environmental, cultural and policy factors could contribute to impaired physical activity in chronic disease [3].

Previous research has shown that the impairment in activity is progressive as activity levels in COPD patients further decreases over time [26;34]. In only two of the studies included in this review, patients with COPD reported their activity levels [16;22]. Interestingly, their activity levels were higher compared with previous findings reported in literature [34]. A potential explanation may be that physical activity was self-reported in the studies included in our review, while the lower levels in the literature were objectively measured by a validated accelerometer. Of self-reported physical activity, it is known that it is often misjudged by participants; patients tend to underestimate standing time and overestimate walking time [35]. Therefore, the use of objective measures, such as accelerometers to adequately assess physical activity is recommended [36].

The present review showed that limitations in physical activity due to morning symptoms can be significantly reduced with medical treatment. This conclusion is based on two obser-

vational studies and one study that pooled two large phase III, double-blind, randomised, parallel-group active- and placebo-controlled study. Despite two out of three studies being observational studies without a prespecified intervention and a change of recall bias, all conclusions pointed in the same direction: medical treatment results in a reduction of physical activity limitations and a reduction of morning symptoms. This is in line with other studies that found positive effects of pharmacotherapy on symptoms and morning routines [37-39]. These studies were not included in this review, since the authors did not examine the association between morning symptoms and physical activity. Therefore, it is unclear whether the improvements in physical activities were the result of improvements in symptoms or the other way around, or if these effects are independent from each other.

One of the potential limitations of this review is that the search strategy could have missed some articles about morning symptoms if morning symptoms were not adequately highlighted in the abstract. However, this is unlikely because cross-references of the included articles were carefully checked as well. Another limitation of this review is the use of the STROBE and CONSORT checklists as a quality checklist for the included studies. These checklists were not developed to score the quality of reviews, but were developed as checklists to strongly report original studies. Therefore, there is no consensus when an article may be indicated has high or low and arbitrary rules are used to assess the quality. Another limitation of the included studies could be that some patients included in the studies had asthma. In most included articles, asthma was an exclusion criterion and only one study did not exclude patients with other lung diseases. In that study, 37% of the included patients had self-reported asthma as a co-diagnosis [19]. Also, it is possible that patients in the included studies have been misdiagnosed or wrongly coded as COPD patients. In one included study, 12.9% of patients had never smoked [20], which makes the diagnosis of COPD much more unlikely. It is presumable that the more asthma patients were wrongly included, the more morning symptoms occurred, since circadian variation of lung function and symptoms is well described in asthma [40]. Nevertheless, in COPD patients, symptoms vary as well, even with daily and weekly variation [21;40]. More than half of patients experience COPD symptoms throughout the whole 24-h day [16] and only a few patients experienced solely morning symptoms. The morning is the most troublesome part of the day with limitations in activities, probably due to circadian variation in lung function or because the morning is the most active period of the day. The night is the second most troublesome part of the day for patients with COPD [41;42]. Another limitation is that most included articles were observational studies, with potential recall bias; patients might inadequately report some events or symptoms. Two of the observational studies were internet surveys [19;21]. Important limitations of internet surveys are that data is self-reported and there might be selection bias, since not all patients have access to internet, and internet access is influenced by age, social status and employment status.

This may result in a younger population and a higher socio-economic status. Two of the included studies [19;21] recruited patients from consumer panels. This might cause "self-selection bias" and the included patients are probably not representative for the whole COPD group. In one study [18], 94.7% of included patients were male and results of this study cannot be generalised to females.

In conclusion, across all disease stages, COPD patients experience morning symptoms that are negatively associated with physical activity. However, it is not possible to prove causality yet, because of the observational designs of these studies. The important finding that morning symptoms are negatively associated with morning symptoms suggests that physicians should include the evaluation of morning symptoms in their clinical assessment and they should include the control of morning symptoms as a goal of treatment, since there is evidence that treatment has positive impact on morning symptoms. There is also some evidence that pharmacotherapy improves morning symptoms and possibly reduces the degree of activity limitations by reducing morning symptoms. Up until now, studies using objective evaluations of physical activity levels and the association with morning symptoms are lacking. Future studies, preferably prospective randomised trials, should focus on objectively measured physical activity in COPD patients especially in the morning. We also recommend validation of a tool to evaluate morning symptoms, because a validated tool is lacking. If more evidence supports the finding that morning symptoms and physical activity are related, these factors will be more emphasized and will find a place in guidelines and statements.

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LIST OF ABBREVIATIONS

CCQ: Clinical COPD Questionnaire
CONSORT: Consolidated Standards of Reporting Trials
COPD: Chronic obstructive pulmonary disease
GOLD: Global Initiative for Chronic Obstructive Lung Disease
LABA: long acting beta-agonist
LAMA: long-acting muscarinic antagonist
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE: STrengthening the Reporting of OBservational studies in Epidemiology

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SUPPLEMENTARY MATERIALS

Supplementary text 1. Full search

Our PubMed search on 27th October 2015 contains of this combination:

((“Pulmonary Disease, Chronic Obstructive”[Mesh] OR “COPD”[tw] OR “Chronic Obstructive Pulmonary Disease”[tw] OR “Chronic Obstructive Pulmonary Diseases”[tw] OR “COAD”[tw] OR “Chronic Obstructive Airway Disease”[tw] OR “Chronic Obstructive Lung Disease”[tw] OR “Chronic Obstructive Airway Diseases”[tw] OR “Chronic Obstructive Lung Diseases”[tw] OR “Chronic Airflow Obstructions”[tw] OR “Chronic Airflow Obstruction”[tw] OR “Chronic Bronchitis”[tw] OR “Pulmonary Emphysema”[tw]) AND (“Morning symptoms”[tw] OR ((morning*[tw] OR “time of day”[tw]) AND (symptom*[tw] OR routine*[tw] OR activit*[tw] OR limitation*[tw] OR complaint*[tw] OR “Signs and Symptoms, Respiratory”[Mesh] OR “Sputum”[mesh] OR “sputum”[tw] OR “cough”[tw] OR cough*[tw] OR breathless*[tw] OR “Shortness of Breath”[tw] OR “Breath Shortness”[tw] OR “short of breath”[tw] OR dyspnea*[tw] OR dyspnoe*[tw] OR “wheezing”[tw] OR “chest tightness”[tw]))) AND (“activity”[tw] OR “activities”[tw] OR “inactivity”[tw] OR “inactivities”[tw] OR “Motor Activity”[Mesh] OR “physical inactivity”[tw] OR “physical activity”[tw] OR “physical activities”[tw] OR “locomotor activity”[tw] OR “locomotor activities”[tw] OR “motor activity”[tw] OR “motor activities”[tw] OR “Exercise”[tw] OR “Circuit-Based Exercise”[tw] OR “Cool-Down Exercise”[tw] OR “Muscle Stretching Exercises”[tw] OR “Physical Conditioning”[tw] OR “Plyometric Exercise”[tw] OR “Resistance Training”[tw] OR “Running”[tw] OR “Jogging”[tw] OR “Swimming”[tw] OR “Walking”[tw] OR “Warm-Up Exercise”[tw] OR “Cataleptic Freezing Reaction”[tw] OR “Tonic Immobility Response”[tw] OR “Pronation”[tw] OR “Supination”[tw] OR “Exercises”[tw] OR “Cool-Down Exercises”[tw] OR “Muscle Stretching Exercise”[tw] OR “Plyometric Exercises”[tw] OR “Warm-Up Exercises”[tw] OR “Human Activities”[Mesh] OR routine*[tw]))

Supplementary table 2. STROBE and CONSORT checklists

STROBE checklist

Section/Topic	Item #	Recommendation	Stephenson [20]	Miravitlles [16]	O'Hagan [19]	Roche [17]	Kim [18]	Kessler [22]	Partridge [21]
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		X			X	X	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	X	X			X	X	X
Introduction									
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	X	X	X	X	X	X	X
Objectives	3	State specific objectives, including any pre-specified hypotheses							
Methods									
Study design	4	Present key elements of study design early in the paper	X	X	X	X	X	X	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X	X	X	X	X		X
Participants	6	Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	X	X	X	X		X	X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X	X	X				X
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	X	X	X	X	X	X	X
Bias	9	Describe any efforts to address potential sources of bias		X	X			X	
Study size	10	Explain how the study size was arrived at		X					
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X	X	X	X	X	X	X
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding				X	X	X	X
		(b) Describe any methods used to examine subgroups and interactions				X		X	X
		(c) Explain how missing data were addressed		X					
		(d) Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy				Not rel.			X
		(e) Describe any sensitivity analyses						X	

STROBE checklist (*continued*)

Section/Topic	Item #	Recommendation	Stephenson [20]	Miravitlles [16]	O'Hagan [19]	Roche [17]	Kim [18]	Kessler [22]	Partridge [21]
Results									
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X				X	X	
		(b) Give reasons for non-participation at each stage						X	
		(c) Consider use of a flow diagram	X				X	X	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X	X	X	X	X	X	X
		(b) Indicate number of participants with missing data for each variable of interest		X		X		X	
Outcome data	15*	Cross-sectional study—Report numbers of outcome events or summary measures	X	X	X	X	X	X	X
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X	X	X	X		X	X
		(b) Report category boundaries when continuous variables were categorized	X	X	X	X		Not rel.	X
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		X		X		Not rel.	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X		X	X	X		X
Discussion									
Key results	18	Summarise key results with reference to study objectives	X	X	X	X	X	X	X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X	X	X	X	X	X	X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, etc	X	X		X	X	X	X
Generalisability	21	Discuss the generalizability (external validity) of the study results	X	X		X			X
Other information									
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X	X	X	X	X	X	X
Total			**18**	**18**	**15**	**16**	**14**	**16**	**17**

STROBE: STrengthening the Reporting of OBservational studies in Epidemiology. *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

CONSORT checklist

Section/Topic	Item #	Recommendation	Bateman [15]
Title and abstract	1	(a) Identification as a randomised trial in the title	X
		(b) Structured summary of trial design, methods, results, and conclusions	X
Introduction			
Background and objectives	2	(a) Scientific background and explanation of rationale	X
		(b) Specific objectives or hypotheses	X
Methods			
Trial design	3	(a) Description of trial design (such as parallel, factorial) including allocation ratio	X
		(b) Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4	(a) Eligibility criteria for participants	X
		(b) Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	X
Outcoumes	6	(a) Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	X
		(b) Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7	(a) How sample size was determined	
		(b) When applicable, explanation of any interim analyses and stopping guidelines	
Sequence generation	8	(a) Method used to generate the random allocation sequence	
		(b) Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11	(a) If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes)	X
		(b) If relevant, description of the similarity of interventions	

CONSORT checklist (*continued*)

Section/Topic	Item #	Recommendation	Bateman [15]
Statistical methods	12	(a) Statistical methods used to compare groups for primary and secondary outcomes	X
		(b) Methods for additional analyses, such as subgroup analyses and adjusted analysesw	X
Results			
Participant flow	13	(a) For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	X
		(b) For each group, losses and exclusions after randomisation, together with reasons	X
Recruitment	14	(a) Dates defining the periods of recruitment and follow-up	
		(b) Why the trial ended or was stopped	

Supplementary table 3. Detailed self-reported limitations due to morning symptoms

First author [ref.]	Limitations in morning activities			Limitations in daily activities
	Self-care	Domestic activities	Work	
Bateman [15]	NA	NA	NA	NA
Stephenson [20]	NA	NA	41.8% of all COPD patients is not working (unclear it is due to morning symptoms)	NA
Miravitlles [16]	NA	NA	NA	NA
O'Hagan [19]	Getting up: 62%[#]; taking a shower: 43%[#]; grooming: 34%[#]; dressing: 43%[#]	Going up and down stairs: 79%[#]; making bed: 55%[#]; making breakfast: 34%[#]; taking children to school: 48%[#]; travelling to supermarket: 56%[#]; morning chores: 70%[#]	41% is not working[#] (unclear it is due to morning symptoms) Travelling to work: 59%[#]	Increased impact on normal daily activities (p=0.007)
Roche [17]	For patients in paid employment, the disease's impact on getting up and ready for the day was significantly higher in those with morning symptoms (2.99 vs. 2.4[§], p<0.001)	NA	70.4% is not working (unclear it is due to morning symptoms) Higher impact during the working day in patients with morning symptoms (2.86 vs. 2.51[§], p=0.027)	Limits the amount of housework I can do: 66%[‡] Means that I am tired throughout the rest of the day: 64%[‡] Means that I do not make commitments before a certain time: 33%[‡] Means that I cannot go grocery / supermarket shopping: 27%[‡]
Kim [18]	Getting out of bed: 82.9%[#]; washing yourself: 76.3%[#]; dressing yourself: 70%[#]; using the toilet: 77.6%[#]; drying yourself: 77.6%[#]; eating breakfast: 56.6%[#]	Preparing breakfast 44.7%[#]	NA	NA

Supplementary table 3. Detailed self-reported limitations due to morning symptoms (*continued*)

First author [ref.]	Limitations in morning activities			Limitations in daily activities
	Self-care	Domestic activities	Work	
Kessler [22]	Washing 41.0%; dressing 40.7%; drying 36.2%; getting out of bed 35.4%	NA	NA	Going up and down stairs 82.5%; doing heavy household chores 56.9%; going shopping 43.1% doing sport or hobbies 35.9%
Partridge [21]	Severity score[¶] in severe/non severe[+] COPD. Putting socks on 6.7/4.4; showering 6.1/3.8; drying 6.1/3.8; getting dressed 6.0/3.8; getting out of bed 4.5/3.0; washing yourself 4.7/3.0; preparing breakfast 4.4/3.0; eating breakfast 3.8/2.7; cleaning your teeth 3.5/2.4	Severity score[¶] in severe/non severe[+] COPD. Walking up/down stairs 8.6/6.2; making the bed 6.8/4.3; walking around the house in the morning 5.4/3.5; washing dishes 5.0/3.3; going to the bathroom 4.2/2.6	NA	NA

[#]: In patients with morning symptoms; [¶]: Rated on a scale from 1 to 10, where 1= it is not affected at all and 10 = it is greatly affected; [+]"Severe" was defined in this study as: regular use of chronic obstructive pulmonary disease (COPD) medication plus a third level of breathlessness or above using Medical Research Council dyspnoea scale and one or more exacerbations in the preceding 12 months; [§]: Measured on a 7-point Likert scale of 0=no impact to 7=constant impact; [‡]: % of COPD patients whose rest of days are impacted by morning symptoms

The association between objectively measured physical activity and morning symptoms in COPD

Authors

Amanda R. van Buul[1]
Marise J. Kasteleyn[1,2]
Niels H. Chavannes[2]
Christian Taube[1,3]

Affiliations

[1]Dept of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands.
[2]Dept of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands.
[3]Dept of Pulmonary Medicine, West German Lung Center, Essen University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany

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ABSTRACT

Purpose: The morning is the most bothersome period for COPD patients. Morning symptom severities in different Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages are not well studied. Furthermore, factors that are associated with morning symptoms, especially the associations with objectively measured physical activity are also not well described.

Materials and methods: The aim of this cross-sectional observational study was to assess morning symptom severity in GOLD A, B, C and D patients, according to the definitions of the GOLD 2015 statement. Morning symptoms were assessed with the PRO-Morning COPD Symptoms Questionnaire. Differences in morning symptom severity between different COPD stages were assessed with a one-way analysis of variance followed by post hoc analyses. The association between dyspnea severity (assessed with the modified Medical Research Council scale), health status, airflow limitation, lung hyperinflation, anxiety and depression, inflammatory parameters, exacerbations, objectively measured physical activity parameters retrieved from accelerometry and morning symptom severity was evaluated using linear regression analysis.

Results: Eighty patients were included (aged 65.6±8.7 years, forced expiratory volume in 1 second [FEV_1] %predicted 55.1±16.9). Mean (±SD) morning symptom score was 19.7 (±11.7). Morning symptom severity was significantly different between COPD stages: mean (±SD) score in GOLD A was 9.7 (±7.2), in GOLD B 19.8(±10.7), in GOLD C 8.6(±9.3) and in GOLD D 23.8(±11.2) ($p<0.001$). Lower health status, more symptoms, increased anxiety and depression, less physical activity (all $p<0.001$) and lower FEV_1 ($p=0.03$) were associated with an increased morning symptom severity.

Conclusion: Patients with overall more symptomatic COPD have significant higher morning symptom scores. Morning symptom severity was associated with important clinical outcomes: lower health status, more symptoms, increased anxiety and depression, fewer steps a day, less time in moderate and vigorous physical activity with bouts of at least 10 minutes and lower FEV_1. The data suggest that morning symptoms should be carefully assessed in addition to assessments by general COPD-specific questionnaires, especially in those with more symptomatic COPD. More research is needed on potential therapies to improve morning symptoms; this study shows potential targets for intervention.

Keywords: accelerometry, chronic obstructive pulmonary disease, physical activity, PRO-Morning COPD Symptoms Questionnaire, morning symptoms

INTRODUCTION

COPD is the fifth leading cause of disability-adjusted life-years worldwide.[1] COPD is characterized by airway obstruction, lung emphysema and chronic inflammation of the airways. Airway obstruction is usually progressive over time but variability over short time is low. Still, COPD symptoms vary throughout the day.[2] In recent years, it has become apparent that the morning is the most symptomatic part of the day for most COPD patients.[3] A recent review showed that the occurrence of morning symptoms in COPD varies widely from 38.9% up to 94.4% of patients and morning symptoms are present in all COPD severity classes.[4] However, the prevalence of morning symptoms seems to be heavily dependent on the used questionnaire.[5] In addition, few studies assessed the severity of morning symptoms in relation to COPD severity and identified factors that are associated with morning symptoms.[2, 6, 7]

One of the important factors in COPD patients is physical activity. People with COPD are more physically inactive compared to their healthy peers.[8, 9] This is also reflected in the observation that only 26% to 30% of patients with COPD fulfilled the WHO physical activity recommendations.[10, 11] The lack of sufficient physical activity is associated with more exacerbations, hospitalizations, all-cause mortality[12] and lower quality of life.[13] The aetiology of physical inactivity in COPD patients is not completely understood. The lack of activity could be due to the avoidance of pulmonary symptoms or it can be speculated that physical activity could be a risk factor to develop COPD. Self-reported low physical activity has been shown as a factor that is related with morning symptoms.[2] Half of the patients reported that they had made changes in morning routines, even in simple tasks, due to symptoms.[14] However, to our knowledge, no studies have been done that evaluate the relationship between objectively measured physical activity by triaxial accelerometry and morning symptoms.

The primary objective of the Morning symptoms in-Depth observAtional Study (MODAS) was to assess the severity of morning symptoms in different Global Initiative for Obstructive Lung Disease (GOLD) stages. The secondary objective was to evaluate the association between dyspnea severity, health status, airflow limitation, lung hyperinflation, anxiety and depression, inflammatory parameters, exacerbations, objectively measured physical activity parameters and morning symptom severity. We hypothesized that patients in more advanced GOLD stages have higher morning symptom scores. Furthermore, we expect that morning symptom severity will be negatively associated with physical activity.

MATERIALS AND METHODS

Study design

The MODAS was a single center, observational, cross-sectional study that was conducted from September 2015 until February 2017 in the Netherlands. The medical ethics committee from the Leiden University Medical Center (LUMC) approved the study (protocol number NL51951.058.15).

Study subjects

Outpatients were recruited from a university medical center (the LUMC), a regional hospital (the Alrijne hospital) and were recruited by distributing flyers in local papers. Interested patients received the study information by letter. Upon agreeing to participate, a visit was scheduled. All patients gave written informed consent.

Patients were eligible if they had a diagnosis of COPD by a physician, met the criteria for GOLD II-IV according to the definitions of the GOLD statement[15] and were aged 40 to 80 years, a general symptomatic patient group. Furthermore, they had to be current smokers or ex-smokers with a lifetime tobacco exposure of ≥10 pack years. Patients were excluded if they had a diagnosis of asthma, history of sensitization to allergens or significant other lung disease. In addition, patients were excluded if they had comorbidities that significantly impaired exercise capacity in the opinion of the investigator (severe polyneuropathy, leg amputation). Other exclusion criteria were current malignant diseases or clinical signs of acute heart failure. Patients with mental impairment that could result in noncompliance with the study protocol were also excluded. Also, patients who were currently enrolled in a rehabilitation program or with an exacerbation in the previous 2 months were excluded. An exacerbation was defined as sustained worsening of respiratory symptoms during 48 hours and requiring oral corticosteroid, antibiotic or a combination of this treatment that was initiated by a physician, a visit to the emergency department or hospitalization with or without intensive care visit. Respiratory symptoms included at least one of the Anthonisen criteria (increased dyspnea, sputum volume and sputum purulence).[16]

Study procedures and outcomes

The study consisted of one visit to the study center. Patients were interviewed by a physician about their employment status, smoking status and COPD exacerbations in the previous year. Furthermore, morning symptoms, dyspnea severity, health status and pulmonary function were assessed and blood was drawn. All pulmonary function tests were performed between 8.30 and 11.00 AM. Immediately following this visit the patients wore a triaxial accelerometer for 7 consecutive days. To collect information regarding possible adverse events patients were contacted by telephone after these 7 days.

The occurrence and severity of morning symptoms were assessed with the PRO-Morning COPD Symptoms Questionnaire.[17] This questionnaire consists of six questions. Patients rated the severity of dyspnea, sputum production, chest tightness, wheezing and cough in the morning with a Likert scale ranging from 0 to 10 points for each question. 0 points represent no symptoms and 10 points represent symptoms as severe as they can imagine. Limitations in the morning due to COPD were scored with the same Likert scale. Total morning symptom scores ranged from 0 to 60. A total score of 0 indicated no symptoms at all in the morning.

The American College of Sports Medicine (ACSM) and the American Heart Association stated that adults should perform moderate-intensity physical activity for a minimum of 30 minutes (or bouts of at least 10 minutes) for 5 days each week or vigorous-intensity physical activity for a minimum of 20 minutes on 3 days each week.[18] To objectively measure physical activity, patients wore a validated triaxial accelerometer (Dynaport MoveMonitor, McRoberts BV, The Hague, the Netherlands)[19-21] 24 hours a day for 7 consecutive days after baseline visit. Due to non-water resistance, patients were not allowed to wear the accelerometer while taking a shower or a bath. Body posture and types of physical activity, as well the duration and intensity of the activity were measured. Steps, total duration of active and inactive periods, active time in light (1.5-3.0 metabolic equivalent task [MET]), moderate (3.0-6.0 MET) and vigorous-intensity (6.0-9.0 MET) activities, number of active and inactive periods and number of walking periods ≤10 seconds, 10 to 20 seconds and >20 seconds were taken as secondary outcomes derived from the accelerometer. Additionally, to take the activity guidelines of the ACSM into account, active time in moderate physical activity (MPA), vigorous physical activity and moderate-to-vigorous physical activity (MVPA) in bouts of at least 10 minutes were measured. Activity was defined as standing, shuffling and walking combined; inactivity was defined as sitting and lying combined. Furthermore, the accelerometer measured the time that it was not worn.

Symptom burden was assessed with the modified Medical Research Council (mMRC) scale with scores ranging from 0 to 5.[22] Health status was assessed using the COPD assessment test (CAT).[23] Comorbidity was evaluated with the Charlson Comorbidity index (CCI).[24] High-sensitive C-reactive protein was measured in serum. Total leukocyte cells counts as well as absolute numbers of eosinophils were assessed. Lung function was assessed post-bronchodilator via spirometry (CareFusion, Masterscreen PFT System) following European Respiratory Society (ERS)/American Thoracic Society (ATS) standards.[25] Forced vital capacity (FVC) and forced volume in one second (FEV_1) were expressed in absolute and % predicted values, respectively (based on Global Lung Function Initiative 2012).[26] Total lung capacity and residual volume (RV) were measured by body box (Carefusion, Masterscreen Body)[27] and RV was expressed in % predicted values (based on European

Community for Coal and Steel). To assess hyperinflation, the ratio between RV and TLC was calculated. Severity of COPD was reported as GOLD A-D based on symptoms assessed with the mMRC, airway obstruction and exacerbations in the previous year[15] (Supplementary materials).

Statistical analysis

Descriptive data were reported as mean values ± standard deviations (SD) for continuous data with a normal distribution, median with interquartile ranges (IQR) for continuous data with a non-normal distribution or percentages for categorical data. To assess whether there was a normal distribution, histograms were made from each continuous individual variable and the shapes of the histograms were carefully assessed. Differences for age and gender between participants and nonparticipants were analyzed with an independent *t*-test and a chi-square test respectively. Differences in morning symptom severity between COPD stages A, B, C and D were assessed with a one-way analysis of variance followed by post hoc analyses.

When the accelerometer was worn less than 22.5 hours a day (94%), the day was excluded from analysis. Mean values derived from the accelerometer were calculated as the mean per patient only from valid days. When there was an adverse event for which a health care provider visit was required during the study period, the patient was excluded from activity analysis since adverse events might have negative effects on physical activity. The association between physical activity, dyspnea severity, health status, anxiety and depression, airflow limitation, lung hyperinflation, laboratory results, the presence of at least one exacerbation in the previous year and morning symptom severity was analyzed with univariable linear regression analysis. We looked at the overall explained variance (R^2) of morning symptoms. In addition, regression analyses were adjusted for gender, age, ethnicity, body mass index, current smoking, number of exacerbations in the previous year, long-acting muscarinic antagonist (LAMA) use since LAMAs probably protect against morning symptoms[17], employment status and comorbidity measured with the CCI. Missing data were not replaced. For all analyses, a p-value of <0.05 was considered statistically significant. We used SPSS version 23 for the statistical analysis**.**

A sensitivity analysis was performed to examine the impact of the CAT instead of mMRC to calculate GOLD classes A-D since previous studies reported that the use of different questionnaires to categorize COPD patients can significantly alter the groups.[28, 29]

RESULTS

Patients

Of the 168 eligible patients who received the patient information letter, 80 patients agreed to participate. No significant differences between participants and nonparticipants were observed for age (mean [±SD] 65.6[±8.7] and 66.3[±8.4] years respectively, p=0.79) and gender (54% and 44.3% males respectively, p=0.22). No patient dropped out of the study (Figure 1). Table 1 shows demographics and baseline characteristics of the participants. Patients had an airflow obstruction with an average FEV_1 of 55.1% predicted and 26% of the patients were current smokers.

Morning symptoms

Morning symptoms were present in 96% (77/80) of the patients. Mean (±SD) total severity score for morning symptoms was 17.9(±11.7) (Table 2). The most severe symptoms in the morning were dyspnea, cough and sputum production. Overall, 85.0% of all included patients reported physical activity limitations in the morning due to morning symptoms. Morning symptom scores were significantly different between patients with different COPD stages: mean (±SD) score in GOLD A was 9.7(±7.2), B 19.8(±10.7), C 8.6(±9.3) and D 23.8(±11.2) (F [df] = 10.3 [79], p<0.01) (Figure 2). Post hoc analyses showed differences between groups A and B (p <0.01), A and D (p<0.01), B and C (p=0.013) and C and D (p<0.01).

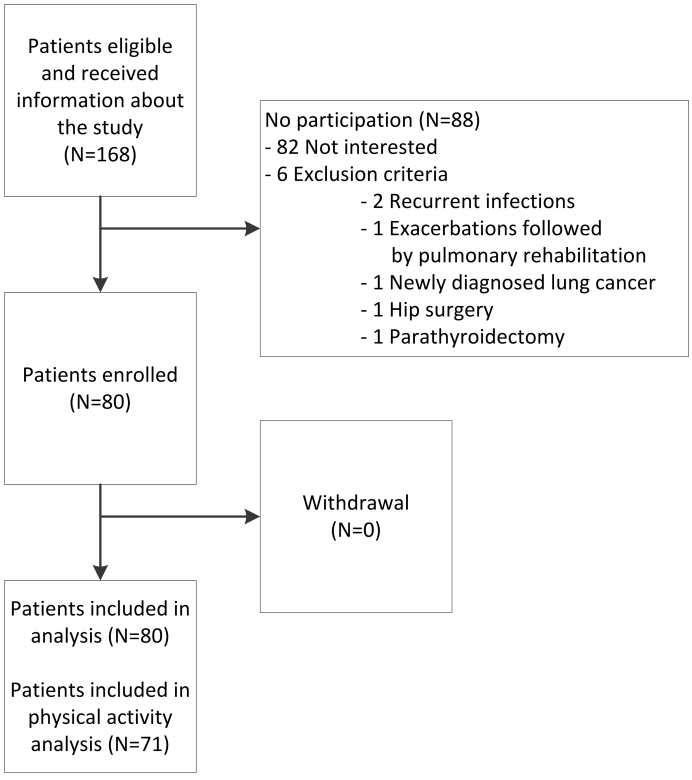

Figure 1 Study flow diagram

Table 1 Baseline characteristics

Characteristic	COPD patients (N = 80)
General	
Age in years, mean (SD)	65.6 (8.7)
Male, n (%)	43 (54%)
Caucasian ethnicity, n (%)	79 (99%)
Current smoking, n (%)	21 (26%)
Pack years, mean (SD)	42.2 (26.8)
Patients with exacerbation(s) in previous year, n (%)	42 (53%)
In current employment n, (%)	22 (28%)
BMI in kg/m^2, mean (SD)	26.3 (5.1)
Lung function (post-bronchodilator)	
FEV_1 %predicted, mean (SD)	55.1 (16.9)
FVC in L, mean (SD)	3.5 (1.0)
RV %predicted, mean (SD)[#]	143 (42)
RV/TLC, mean (SD)[#]	117 (24)
GOLD stage	
GOLD A n, (%)	20 (25%)
GOLD B n, (%)	21 (26%)
GOLD C n, (%)	7 (9%)
GOLD D n, (%)	32 (40%)
Laboratory	
Leucocytes in $x10^9/L$, mean (SD)	8.3 (2.5)
Eosinophils in $x10^9/L$, median [IQR]	0.16 [0.11-0.22]
HsCRP in mg/L, median [IQR]	2.41 [0.26-5.42]
Medication	
ICS, n (%)	6 (8%)
LABA, n (%)	19 (24%)
LAMA, n (%)	60 (75%)
ICS+LABA, n (%)	50 (63%)
LABA+LAMA, n (%)	7 (9%)
Oral corticosteroids, n (%)	3 (4%)
Questionnaires	
CAT total score, mean (SD)	16.5 (7.3)
mMRC total score, mean (SD)	2.4 (1.3)
CCI (total score), median [IQR]	2.0 [1.0-3.0]
Myocardial infarction n, (%)	5 (6%)
Cerebrovascular disease n, (%)	10 (13%)
Uncomplicated diabetes mellitus n, (%)	9 (11%)
Moderate to severe chronic kidney disease n, (%)	6 (8%)
History of solid tumor without metastasis n, (%)	15 (19%)
HADS total score, mean (SD)[#]	9.2 (5.7)

Table 1 Baseline characteristics (*continued*)

Characteristic	COPD patients (N = 80)
Depression	4.7 (3.8)
Anxiety [#]	4.5 (3.2)

BMI: body mass index; CAT: COPD assessment test; CCI: Charlson co-morbidity index; COPD: chronic obstructive pulmonary disease: FEV_1, Forced expiratory volume in 1 second: FVC, forced vital capacity; GOLD: global initiative for obstructive lung disease; HADS: hospital anxiety and depression scale; hsCRP: high sensitive C-reactive protein; ICS: inhaled corticosteroids; IQR: interquartile range; LABA: long acting beta2 agonist; LAMA: long acting muscarinic antagonist; mMRC: modified medical research council; RV: residual volume; SD: standard deviation; TLC: total lung capacity. [#]: For some variables data were missing: HADS (two patients did not fill out all questions about anxiety); body plethysmography (three patients were not able to produce reproducibly curves and 1 patient had claustrophobia).

Physical activity

Eight patients reported an adverse event during the study period (Supplementary table 1) and one patient wore the accelerometer for an insufficient time each day of the study (7.2 to 13.7 hours a day). Ninety-four percent of the measured days from the remaining 71 patients were included in the analysis. The median number of days analyzed per patient was seven. Table 3 shows outcomes derived from accelerometry. Patients walked an average of 5.754 steps a day and they spent 11.4 minutes a day in MVPA with bouts of at least 10 minutes.

Relationship between morning symptoms and other parameters

Table 4 shows the association between baseline patient characteristics and morning symptom severity. When adjusted for confounders, lower health status (estimated regression coefficient =1.194, 95% CI 0.923 to 1.465), higher symptomatic burden (estimated re-

Table 2 Occurrence and severity of morning symptoms

Morning symptoms	N = 80
Total score (range 0-60)[#], mean (SD)	17.9 (11.7)
Number of patients without symptoms and limitations	3 (3.8%)
Sub-items [¶]	
Dyspnea	4.0 [1.3-6.0]
Sputum	2.0 [0.0-5.0]
Chest tightness	0.0 [0.0-2.8]
Wheezing	1.0 [0.0-3.0]
Cough	3.0 [1.0-4.8]
Limitations in the morning due to COPD	4.5 [2.0-7.0]

Data are median [IQR], unless otherwise indicated. COPD: chronic obstructive pulmonary disease; IQR: interquartile range; SD: standard deviation. [#]: Morning symptom score was assessed with the PRO-morning COPD questionnaire, [¶]:Score 0 ("no symptoms") to 10 ("most worst symptoms").

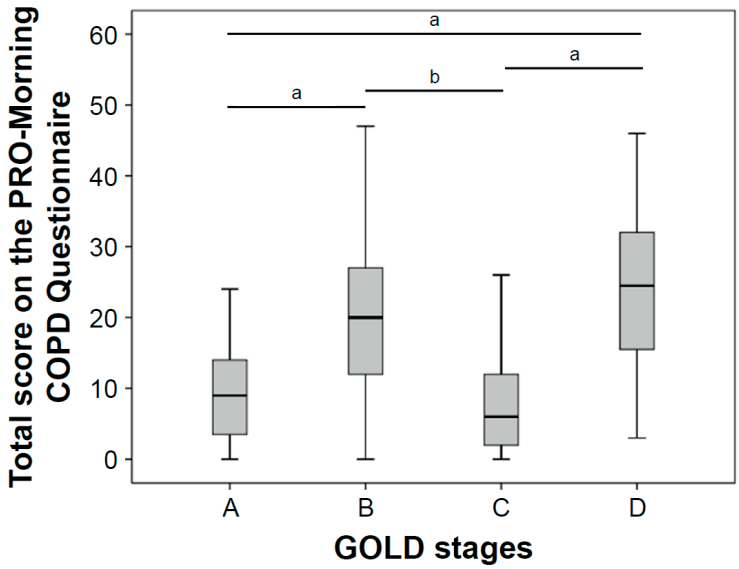

Figure 2 Morning symptom scores in COPD GOLD A, B, C and D groups. COPD GOLD A (N=20), B (N=21), C (N=7), and D (N=32). COPD: chronic obstructive pulmonary disease. GOLD: global initiative for chronic obstructive lung disease. [a]: p<0.01, [b]: p<0.05.

Table 3 Daily physical activity parameters derived from accelerometry

Activity parameters	467 valid days[#] from 71 patients
Inactive parameters[¶]	
Total duration in inactive time in minutes, mean (SD)	1161 (100)
Number of periods in inactive time, mean (SD)	128 (42)
Active parameters[+]	
Steps, mean (SD)	5754 (3553)
Total duration in active time in minutes, mean (SD)	268 (98)
Total duration in light activities in minutes, mean (SD)[§]	80 (33)
Total duration in moderate activities in minutes, mean (SD)[§]	88 (39)
Total duration of vigorous activities in minutes, mean (SD)[§]	0.9 [0.3;6.2]
Mean active time in MVPA with bouts of at least 10 minutes, in minutes, median [IQR)][§]	11.4 [4.4;23.1]
Mean active time in moderate activity with bouts of at least 10 minutes, in minutes, median [IQR][§]	11.5 [4.3;22.1]
Mean active time in vigorous activity with bouts of at least 10 minutes in minutes, median [IQR][§]	0.0 [0.0;0.0]
Number of periods in active time, mean (SD)	1858 (810)
Number of periods walking ≤10 seconds, mean (SD)	317 (139)
Number of periods walking 10-20 seconds, mean (SD)	70 (37)
Number of periods walking >20 seconds, median [IQR]	24 [15;31]

IQR: interquartile ranges; MET: metabolic equivalent task; MVPA: moderate to vigorous physical activity; SD: standard deviation. [#]: valid days were defined as accelerometry for at least 22.5 hours (94%) a day. [¶]: Inactive: sitting and lying combined. [+]: Active: standing, shuffling and walking combined. [§]Light: 1.5-3.0 MET, moderate: 3.0-6.0 MET, vigorous: 6.0-9.0 MET.

Table 4 Associations between health status, dyspnea severity, anxiety and depression, airflow limitation, lung hyperinflation, inflammatory parameters, exacerbations and morning symptom severity

Outcome	Morning symptom score[#] (N=80)				Adjusted[+] morning symptom score[#] (N=80)			
	R^2	Regression coefficient	95% CI	p	R^2	Regression coefficient	95% CI	p
CAT	0.62	1.268	1.042;1.494	<0.001	0.67	1.194	0.923;1.465	<0.001
mMRC	0.30	4.991	3.270;6.712	<0.001	0.47	4.193	2.384;6.002	<0.001
HADS[¶]	0.33	1.152	0.776;1.528	<0.001	0.51	1.098	0.706;1.490	<0.001
FEV_1 (% predicted)[§]	0.06	-0.173	-0.325;-0.021	0.026	0.35	-0.170	-0.324;-0.017	0.030
RV/TLC [¶,§]	0.04	0.094	-0.019;0.207	0.10	0.34	0.063	-0.050;0.176	0.27
HsCRP	0.03	0.456	-0.128;1.039	0.12	0.31	0.242	-0.319;0.804	0.39
Leucocytes	0.02	0.656	-0.383;1.695	0.21	0.31	0.217	-0.801;1.236	0.67
Eosinophils	0.06	-14.68	-28.14;-1.231	0.033	0.32	-7.772	-20.575;5.032	0.23
At least one exacerbation in the previous 12 months	0.07	6.302	1.239;11.37	0.015	0.30	01.112	-8.539;6.314	0.77

CI: confidence interval; CAT: COPD assessment test; FEV_1: Forced expiratory volume in 1 second; HADS: hospital anxiety and depression scale; hsCRP: high sensitive c-reactive protein; LAMA: long-acting muscarinic antagonist; mMRC: modified medical research council; R^2: explained variance; RV: residual volume; TLC: total lung capacity. [#]: Morning symptoms were assessed with the PRO-morning COPD questionnaire, [¶]: For some variables data were missing: HADS (two patients did not fill out all questions about anxiety); body plethysmography (three patients were not able to produce reproducibly curves and 1 patient had claustrophobia). [+]: Adjusted for gender, age, ethnicity, body mass index, smoking, number of exacerbations, LAMA use, employment and comorbidity. [§]: Post bronchodilator.

gression coefficient =4.193, 95% CI 2.384 to 6.002), increased anxiety and depression and lower FEV_1 were associated with morning symptom severity. Furthermore, physical activity that was objectively measured by accelerometry was associated with morning symptom severity: fewer steps a day (estimated regression coefficient =-0.001, 95% CI -0.002 to -0.000), less time in MVPA with bouts of at least 10 minutes (estimated regression coefficient =-0.135, 95% CI -0.233 to -0.037) and less time in MPA with bouts of at least 10 minutes (estimated regression coefficient =-0.192, 95% CI -0.321 to -0.064) (Table 5). The explained variance of all studied patient characteristics was highest for the CAT (62%)

Sensitivity analysis

When the CAT was used instead of the mMRC scale to classify COPD severity, differences in the morning symptom severity were still present between the different GOLD stages. In addition, there was also a significant difference in morning symptom severity between patients with COPD GOLD B and D (Supplementary figure 1).

Table 5 Associations between minutes in active and inactive time, periods in activity and inactivity and morning symptom severity

Outcome	Morning symptom score[#] (N=71)[¶]				Adjusted[+] morning symptom score[#] (N=71)[¶]			
	R^2	Regression coefficient	95% CI	p	R^2	Regression coefficient	95% CI	p
Steps	0.09	-0.001	-0.002;0.000	0.013	0.30	-0.001	-0.002;0.000	0.043
Total active time[§]	0.03	-0.019	-0.047;0.009	0.18	0.25	-0.010	-0.039;0.020	0.52
Total inactive time[*]	0.04	0.022	-0.005;0.049	0.11	0.26	0.012	-0.018;0.041	0.43
Light activities[‡]	0.001	0.011	-0.073;0.095	0.79	0.26	0.035	-0.050;0.119	0.42
Moderate activities[‡]	0.08	-0.082	-0.150;-0.014	0.019	0.27	-0.052	-0.150;0.019	0.15
Vigorous activities[‡]	0.03	-0.130	-0.327;0.067	0.19	0.26	-0.097	-0.306;0.112	0.36
Time in MVPA with bouts[‡]	0.13	-0.151	-0.244;-0.058	<0.001	0.33	-0.135	-0.233;-0.037	<0.001
Time in moderate activity with bouts[‡]	0.15	-0.218	-0.344;-0.092	<0.001	0.35	-0.192	-0.321;-0.064	<0.001
Time in vigorous activity with bouts[‡]	0.03	-0.170	-0.387;0.047	0.12	0.26	-0.127	-0.357;0.103	0.27
Number of periods in inactive time[*]	0.01	-0.030	-0.096;0.036	0.37	0.25	0.003	-0.069;0.076	0.92
Number of periods in active time[§]	0.04	-0.003	-0.006;0.001	0.10	0.25	-0.001	-0.004;0.003	0.71
Periods in walking time ≤10 seconds	0.06	-0.021	-0.040;-0.002	0.034	0.26	-0.011	-0.032;0.009	0.28
Periods in walking time 10-20 seconds	0.04	-0.061	-0.134;0.012	0.099	0.26	-0.028	-0.105;0.050	0.48
Periods in walking time >20 seconds	0.07	-0.133	-0.249;-0.017	0.026	0.29	-0.111	-0.232;0.010	0.07

CI: confidence interval; MET: metabolic equivalent task; MVPA: moderate-to-vigorous physical activity; R^2: explained variance.[#]: Morning symptoms were assessed with the PRO-morning COPD questionnaire, [¶]: Data from patients with an adverse event (N=8) or patients with no valid data from accelerometry (N=1) were excluded. Analyses were performed on data from 71 patient. [+]: Adjusted for gender, age, ethnicity, body mass index, smoking, number of exacerbations, LAMA use, employment and comorbidity [§]: Active: standing, shuffling and walking combined. [*]: Inactive: sitting and lying combined. [‡]: Light: 1.5-3.0 MET, moderate: 3.0-6.0 MET, vigorous: 6.0-9.0 MET.

DISCUSSION

In the present study morning symptom severity was assessed in COPD GOLD A, B, C and D patients. Furthermore, the association between patient characteristics with special focus on physical activity and morning symptom severity was studied. As far as we know, this is the first time the relationship between morning symptom severity and objective measures of the physical activity by triaxial accelerometry has been studied. In the present study, patients with overall more symptomatic COPD had significant higher morning symptom scores. Lower health status, higher symptomatic burden, increased anxiety and depression,

lower FEV_1 and fewer steps a day and less time in moderate and vigorous physical activity with bouts of at least 10 minutes that was objectively measured by accelerometry were associated with morning symptom severity.

Morning symptom scores were higher in patients with GOLD B and D compared with GOLD A and C stages. However, morning symptoms were not limited to more advanced COPD stages and were also present in patients of group A. These results are in line with the first and so far only study that described the relation between the occurrence of morning symptoms and severity of COPD with GOLD A-D classification.[7] In that study, patterns of morning symptom occurrence was more associated with the GOLD A-D categorization compared to GOLD 1-4 classification. GOLD 1-4 classification is based only on airflow limitation, whereas in GOLD A-D a combination of airflow limitation, general symptoms and exacerbations are used to classify the patients. Previous studies have shown associations between morning symptoms and airflow limitation,[2, 30] general symptoms [2, 3] and COPD exacerbations in the previous 12 months.[30-32] In the current study FEV_1 and symptoms measured with the mMRC were significantly associated with the severity of morning symptoms. Furthermore, unadjusted analyses showed an association between exacerbations in the previous 12 months and morning symptom severity. Since overall symptoms and exacerbations, which are included in the GOLD A-D scheme, are associated with morning symptoms, we believe that GOLD A-D relates more closer to morning symptoms than GOLD 1-4. The sensitivity analyses showed that the differences in morning symptom severity between GOLD A, B, C and D groups were independent of the symptoms scale that was used and no difference between mMRC and CAT was found. Overall, our results are supported by the finding that the occurrence of nighttime symptoms was more closely related to the GOLD A-D classification than the GOLD 1-4 classification.[33]

In the present study, the occurrence of morning symptoms was higher than that reported in other studies. The use of a different morning symptoms questionnaire could be responsible for the higher occurrence in the current study.[5] The prevalence of morning symptoms in the present study is in line with a previous trial that studied morning symptoms in more than 3,000 COPD patients.[34] In that study, 94.4% of patients with moderate to severe COPD suffered from morning symptoms, measured with Early-Morning Symptoms of COPD Instrument. In the current study, the PRO-morning symptoms questionnaire was used. One previous randomized trial used this questionnaire and found a mean morning symptom severity score of 16.7.[17] The MODAS showed a slightly higher mean morning symptom score. This could be due to a slightly different COPD population (lower FEV_1, fewer males, less current smokers) or the unknown variance of the morning symptom score. Overall, morning symptoms score are relatively low. For example, analyses on 3,394 COPD GOLD II and III patients have shown a mean morning symptom score of 1.3

(minimum 0; maximum 4).[34] Furthermore, we know from previous research that patients underestimated their symptoms and one third of patients who describe their symptoms as being mild to moderate are not able to leave the house due to breathlessness.[35] We think that the PRO-Morning COPD Symptoms Questionnaire can be a suitable tool to assess morning symptoms. Nevertheless, this questionnaire needs to be validated in further studies. Using a validated questionnaire with cutoff scores might help to indicate whether a score of 17.9 could be seen as high or as low impact.

Previous studies that reported the association between morning symptoms and physical activity used self-reported physical activity questionnaires to evaluate physical activity.[2, 3, 6, 14, 30, 34, 36, 37] However, it is known that self-reported outcomes show discrepancies to objective measured outcomes[38] and therefore we assessed physical activity using an established activity monitor.[19, 39] Indeed, when analyzing the data retrieved from these monitors we found a relationship between objectively measured physical activity and an increase in morning symptom severity. More specifically, an association between fewer steps a day, less time in MVPA with bouts of at least 10 minutes and less time in MPA with bouts of at least 10 minutes and increase in morning symptom severity was found. Interestingly, when we do not take these bouts into account, time in MPA and MVPA was not associated with morning symptom severity. This means that COPD patients with higher morning symptom scores are able to perform physical activity of moderate and vigorous intensity similar to those with less severe morning symptoms, but they rarely perform this activity longer than 10 minutes at a time. We suggest that these patients do not perform activities for increased amounts of time as an adaptation to, for example, avoid symptoms and they are therefore not used to being active for more than 10 minutes in moderate or vigorous activity. For light-intensity physical activity, no association with morning symptom severity was found. Sufficient physical activity is important for COPD patients because the lack of it is associated with more exacerbations, hospitalizations, all-cause mortality[12] and lower quality of life.[13] These results together underline the importance of morning symptoms and physical activity. Together, they seem to be a new important target for therapy.

The association between lower health status,[2, 7, 30, 37, 40] more dyspnea,[2, 3] increased anxiety and depression,[2, 30, 37, 40] lower FEV_1[2, 30] and morning symptoms have been described earlier. The association between morning symptoms and overall symptoms might appear to be trivial, however, previous studies have shown that symptoms can vary over the day and therefore more precise assessment of symptoms seems necessary. The present study confirms this; the CAT does not fully cover morning symptoms with an explained variance of 62%. Based on this, we recommend assessing morning symptoms separately

from general symptoms in COPD patients, especially in those with more symptomatic COPD.

A strength of this study is the adjustment for multiple confounders in the regression analysis, which was omitted in previous studies.[2, 37] Furthermore, we believe that this study population is representative of the COPD population since patients were recruited from a variety of sources, namely a university medical center, a regional hospital and recruitment via flyers. This resulted in a heterogeneous COPD patient group. However, the exclusion of COPD GOLD I patients can be seen as a limitation. We expect that including COPD GOLD I patients would result in a slightly lower mean morning symptom score since morning symptoms are also present in mild COPD.[2] However, in this study we decided to focus on more symptomatic patients since it was a cross-sectional study that explored factors that were associated with morning symptoms. One other limitation of this study is that there might be selection bias, since nonparticipants were most likely patients who were not able to come to the study center in the morning. This might have resulted in an underestimation of morning symptoms in the overall COPD population. A limitation for the use of a MoveMonitor was the non-water resistance. For some patients, taking a shower is the most intensive physical activity of the day, and this has not been measured. This resulted in an underestimation of active time. Furthermore, patients were not blinded for the accelerometer. This could have resulted in increased activity since patients felt they were being watched and would not be categorized as "inactive." However, patients took a comparable amount or fewer steps than reported in previous studies[41, 42] suggesting that patients in the MODAS did not adapt their lifestyle to the study. Furthermore, with this observational study design it is not possible to prove causality. Therefore, we are not able to state whether physical activity limitations is a result of morning symptoms, or if it is the other way around: that physical inactivity causes deconditioning which results in an increase of morning symptoms.

CONCLUSION

Patients with overall more symptomatic COPD have significant higher morning symptom scores. Furthermore, morning symptoms were associated with important clinical outcomes: lower health status, more symptoms, increased anxiety and depression, fewer steps a day, less time in moderate and vigorous physical activity with bouts of at least 10 minutes and lower FEV_1. This was the first study that evaluated the relation between morning symptom severity and objective measures of physical activity by triaxial accelerometry. Morning symptoms should be assessed more precisely in addition to assessment by general COPD-specific questionnaires, especially in those with more symptomatic COPD. Therefore, there

is need for the validation of a morning symptom questionnaire. In addition, more research is needed on potential therapies to improve morning symptoms, for example with the improvement of (a combination of) health status, symptoms, anxiety and depression, steps a day, time in moderate and vigorous physical activity with bouts of at least 10 minutes and FEV_1.

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LIST OF ABBREVIATONS

ACSM: American College of Sports Medicine
BMI: body mass index
CAT: COPD assessment test
CCI: Charlson Co-morbidity index
COPD: Chronic obstructive pulmonary disease
ECCS: European Community for Coal and Steel
FEV_1: Forced expiratory volume in 1 second
FVC: Forced vital capacity
GLI: Global Lung Function Initiative
GOLD: Global Initiative for Chronic Obstructive Lung Disease
hsCRP: high sensitive C-reactive protein
ICS: inhaled corticosteroids
IQR: interquartile ranges
LABA: long acting beta2 agonist
LAMA: long acting muscarinic antagonist
MET: metabolic equivalent task
mMRC: modified Medical Research Council
MODAS: Morning symptoms in-Depth observAtional Study
MPA: moderate physical activity
MVPA: moderate-to-vigorous physical activity
R^2: explained variance
RV: residual volume
SD: standard deviation
TLC: total lung capacity

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SUPPLEMENTARY MATERIALS

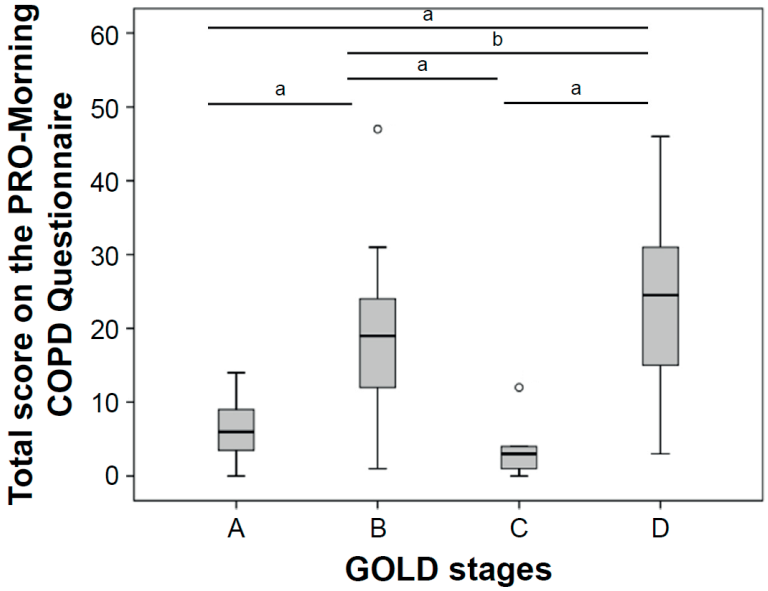
Supplementary text 1

To categorise the patients, the first step was to assess the symptom burden with the mMRC. A low symptom burden was defined as mMRC 0 to 1; a high symptom burden as 2 or higher. Moreover, the exacerbation risk was evaluated by airflow obstruction, number of exacerbations in the previous year and number of exacerbations leading to hospital admission in the previous year. A low risk was defined as a FEV_1 ≥50% and <2 exacerbations a year and no hospital admission due to exacerbation COPD; a high risk was defined as a FEV_1 <50% or ≥2 exacerbations in the previous year or ≥1 hospital admission due to exacerbation COPD. Group A was defined as a low symptom burden with low risk; group B as high symptom burden with low risk; group C as low symptom burden with high risk and group D as high symptom burden with high risk.

Supplementary table 1. Adverse events during study period

Adverse event	Number of patients
Pain in the hand	2
Migraine plus haematuria	1
Flu	1
Pneumonia	1
Exacerbation COPD that was treated by the GP	1
Rhino-sinusitis	1
Exhausted and dyspnoeic for multiple days due to the study visit	1
Total	**8**

COPD: chronic obstructive pulmonary disease; GP: general practitioner.



Supplementary figure 1. Morning symptom scores in COPD GOLD A, B, C and D patients, categorization with CAT. Morning symptoms scores were significant different between patients with COPD GOLD A 6.3 (±4.4), B 18.4 (±10.1), C 4.0 (±4.7) and D 23.6 (±11.0) (F (df) = 13.0 (79), p<0.01). COPD GOLD A (N=12), B (N=29), C (N=5), and D (N=34). CAT: COPD Assessment Test, COPD: chronic obstructive pulmonary disease, GOLD: global initiative for chronic obstructive lung disease. [a]: p<0.01. [b]: p<0.05.

Physical activity in the morning and afternoon is lower in patients with chronic obstructive pulmonary disease with morning symptoms

Authors

Amanda R. van Buul[1]
Marise J. Kasteleyn[1,2]
Niels H. Chavannes[2]
Christian Taube[1,3]

Affiliations

[1]Dept of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands.
[2]Dept of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands.
[3]Dept of Pulmonary Medicine, West German Lung Center, Essen University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany

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ABSTRACT

Background: Patients with chronic obstructive pulmonary disease (COPD) experience symptoms that vary over the day. Symptoms at the start of the day might influence physical activity during the rest of the day. Therefore, physical activity during the course of the day was studied in patients with low and high morning symptom scores.

Methods: This cross-sectional observational study included patients with moderate to very severe COPD. Morning symptoms were evaluated with the PRO-morning COPD Symptoms Questionnaire (range 0–60); the median score was used to create two groups (low and high morning symptom scores). Physical activity was examined with an accelerometer. Activity parameters during the night, morning, afternoon and evening were compared between patients with low and high morning symptom scores using independent t-tests or Mann-Whitney U tests.

Results: Seventy nine patients were included. Patients were aged (mean ± SD) 65.6 ± 8.8 years with a mean forced expiratory volume in 1 s of 55 ± 17%predicted. Patients with low morning symptom scores (score < 17.0) took more steps in the afternoon ($p = 0.015$) and morning ($p = 0.030$). There were no significant differences during the evening and night.

Conclusion: Patients with high morning symptom scores took significantly fewer steps in the morning and afternoon than those with low morning symptom scores. Prospective studies are needed to prove causality between morning symptoms and physical activity during different parts of the day.

Keywords: Afternoon, Chronic obstructive pulmonary disease, Evening, Physical activity, Morning, Morning symptoms

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a worldwide problem with a high prevalence of years lived with disability [1]. COPD is associated with dyspnoea, fatigue and decreased physical activity. Regular physical activity in patients with COPD is associated with a lower risk of admissions and mortality [2]. Most previous studies reported on physical activity during day time solely [3–6]. When physical activity was measured over the course of the day, nuanced reporting on physical activity during different parts of the day was generally lacking [7–10]. Therefore, only little is known about physical activity in COPD patients during the night and early morning. Studying physical activity during the course of the day is important, because a symptomatic start to the day might influence physical activity during the rest of the day.

Patients with COPD experience the morning as most symptomatic part of the day [11, 12] and the night as second most symptomatic part of the day [12]. Studies have shown that morning symptoms are negatively associated with self-reported physical activity [13]. A negative association between morning symptoms and overall physical activity has been reported [14]. However, the relation between morning symptoms and objectively measured physical activity during different parts of the day has not been studied yet. From previous research it is known that morning symptoms influence self-care, housework and work activities [15]. We hypothesized that patients with high morning symptom scores are less active in the morning and during the rest of the day compared to patients with low morning symptom scores. Furthermore, detailed assessments of physical activity over the day could give insight which part might be most suitable for physical activity interventions. Therefore, the primary aim of this study was to examine physical activity during the course of the day depending on morning symptoms. In addition, self-reported physical activity was assessed to better understand which types of activities were generally undertaken.

METHODS

Research design

The Morning symptoms in-Depth observAtional Study (MODAS) was a single centre, observational, cross-sectional study (study NL51951.058.15; www.toetsingonline.nl). The study was conducted from September 2015 to February 2017. The medical ethics committee from the Leiden University Medical Center (LUMC) approved the study protocol.

Participants

Detailed inclusion/exclusion criteria have been reported previously [14]. In summary, included in the study were patients aged 40 to 80 years. A physician had diagnosed them with COPD. They had moderate to very severe airflow limitation according to the Global initiative for Obstructive Lung Disease (GOLD) definitions [16]. Patients were exacerbation-free for at least 2 months. They were current or active smokers with at least 10 pack-years. Main exclusion criteria were the diagnosis of asthma; significant other lung disease, comorbidities and severe pain syndromes that impair exercise capacity. Patients were recruited from the LUMC and Alrijne hospital in Leiden (The Netherlands). Patients who were considered to be eligible were notified about the study by telephone or during an outpatient visit. Furthermore, patients were recruited by flyers in local papers. Eligible interested patients received an information letter. If the patient agreed to participate in the study, a study visit was scheduled. During the visit, written informed consent was obtained.

Assessments

During the baseline visit, demographic data and comorbidities were obtained by a physician. Patients were asked about their medication use and this was verified with a medication overview of the pharmacy. COPD specific health-related quality-of-life, morning symptoms severity, self-reported physical activity and pre- and post-bronchodilator pulmonary function were assessed at the study center. After this visit, patients wore a triaxial accelerometer for seven consecutive days to objectively assess physical activity. When the physical activity measurements were finished, there was a follow-up telephone interview to report possible adverse events.

Morning symptom severity was evaluated with the PRO-Morning COPD Symptoms Questionnaire (pre-morning doses assessment) [17]. This questionnaire consists of six questions about dyspnoea, cough, sputum production, wheezing, chest tightness and limitations in the morning. Patients rated the severity of these symptoms with a Likert scale from 0 to 10 points. 0 for no symptoms; 10 points for symptoms as bad as they can imagine. The total score ranged from 0 to 60.

Physical activity was objectively measured with an accelerometer (Dynaport MoveMonitor, McRoberts BV, The Hague, the Netherlands) [18, 19]. This accelerometer was worn on the waist during the entire day for seven consecutive days resulting in real-life activity recording. To give insight into physical activity over the course of the day, days were divided in four parts of the day of each 6 hours: night (00.00 to 06.00), morning (06.00 to 12.00), afternoon (12.00 to 18.00) and evening (18.00 to 00.00). Duration of activity (standing, shuffling and walking) and inactivity (sitting and lying) in minutes was registered. The number of steps was recorded per part of the day and per hour. Patients were not

allowed to wear the accelerometer during bathing or showering. The duration that the accelerometer was not worn was automatically registered. A measurement was considered valid when patients wore the accelerometer at least 90% per part of the day. Averages of the outcomes of valid parts of the day were calculated for each patient. Patients with only invalid parts of the day were excluded from analysis.

Patients filled out the Dutch version of the international physically activity questionnaire (IPAQ) [20]. In this questionnaire patients reported the number of minutes per day and days per week they were physical active in a 7-day period. Physical activity was categorized in four domains: work, transport, housework or leisure time related. Patients who reported more than 960 min a day each day of the week were excluded from this analysis in line with the activity calculation instructions of the IPAQ.

The Charlson Co-morbidity index was used to evaluate comorbidities (CCI) [21] and the three most common comorbidities were reported as percentage. COPD-specific health-related quality-of-life was assessed with the St George's Respiratory Questionnaire (SGRQ), [22] health status with the Clinical COPD Questionnaire (CCQ) [23] and dyspnoea in daily living with the medical modified research council (mMRC) [24]. All patients performed pre and post-bronchodilator spirometry following ERS/ATS (European Respiratory Society/ American Thoracic Society) standards in the morning between 08.30 and 11.00 (Care Fusion, Masterscreen PFT). [25–27] In this study, reported spirometry outcomes were post-bronchodilator values. Forced volume in 1 second (FEV1) was expressed in % predicted values (based on the Global Lung Function Initiative 2012) [26].

Statistical analysis

Descriptive data were reported as percentages, mean values ± standard deviations (SD) for normal distributed continuous variables and median with interquartile ranges (IQR) for non-normal distributed continuous variables. The study cohort was divided in two equal groups using the median score on the PRO-morning COPD Symptoms Questionnaire as cut-off. Differences in baseline characteristics between the two groups were compared with an independent t-test for continuous normal distributed variables; a Mann-Whitney U test for continuous non-normal distributed variables and chi-square test for categorical variables.

Differences in steps during the total day were compared between patients with low and high morning symptom scores using an independent t-test. Difference in steps and duration of (in)activity during different parts of the day were compared using an independent t-test or Mann-Whitney U test. To give an overview of the number of steps over the course of the day, steps per hour were plotted against hour of the day. Self-reported physical

activity was compared using a Mann-Whitney U test. An explorative subgroup analysis was performed to examine longacting pulmonary medication use. Long-acting pulmonary medication use was categorized in three groups: double bronchodilation (combination of a long-acting beta2 agonist (LABA) and long-acting muscarinic antagonist (LAMA)), a single bronchodilator (LABA or LAMA use) or no use of long-acting pulmonary medication. The difference in mean number of steps in the morning was evaluated with a one way ANOVA.

Steps per hour were plotted against hour of the day for patients with low and high dyspnoea scores in daily living [16] to evaluate the impact of using a general symptom questionnaire instead of a specific morning symptom questionnaire to divide the study group.

A sensitivity analysis was performed to evaluate the impact of adverse events during the study period; all patients who reported an adverse events, defined as self-reported illness or any somatic symptom for which the patient had to visit a health care provider, were excluded from the analyses.

For all analyses, a p-value of < 0.05 was considered statistically significant. Missing data was not replaced. We used SPSS version 23 to perform the analyses.

RESULTS

Patients

From 168 eligible patients who received the patient information form, 80 patients were included in the study and 79 patients had sufficient outcomes from accelerometry for analyses (Figure 1). Table 1 shows demographics and baseline characteristics. Patients were (mean ± SD) 65.6 ± 8.8 years old and 53% were male. They had a mean FEV_1 of 55 ± 17% predicted. Most patients were classified as COPD GOLD D (40.5%) and B (27.8%). Mean morning symptom score was 17.9 ± 11.8 with a range between 0 and 47. The median morning symptom score was 17.0 and was used as cut-off to separate the study cohort in two equal groups (Table 1).

Physical activity

Seventy nine patients wore the accelerometer 7 consecutive days. Thus, data from 553 days were collected from these 79 patients. 95.8% of the night, 91.0% of the morning, 96.7% of the afternoon and 93.9% the evening measurements fulfilled the quality standards and were included in the analysis. In each part of the day, most of the time was spent in inactivity (Table 2).

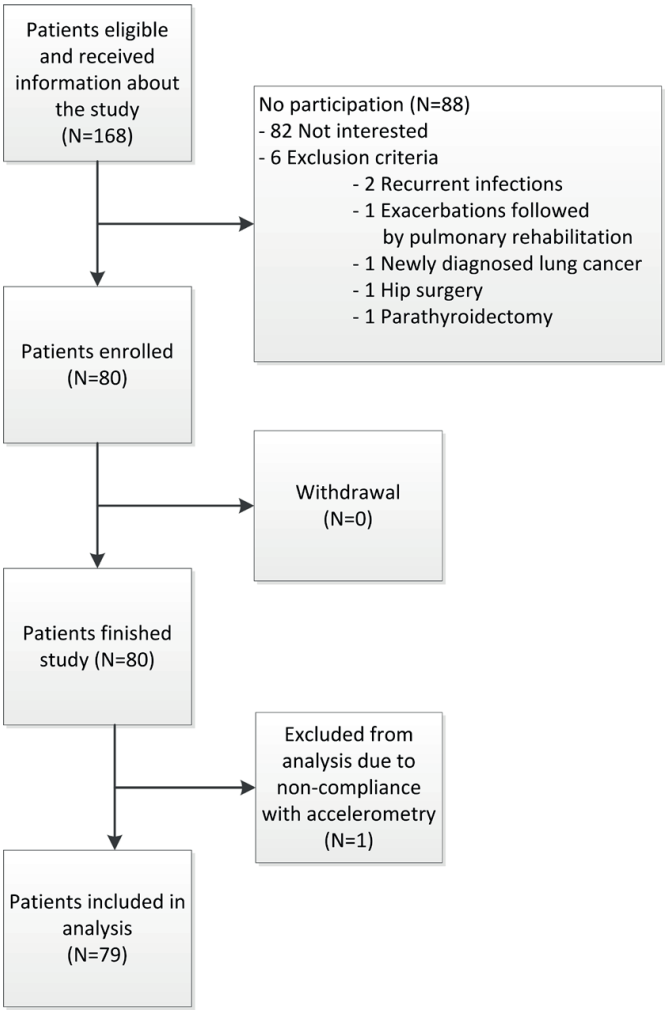

Figure 1 Study flow diagram

Mean number of steps per day was (mean ± SD) 5686 ± 3514. Patients with low morning symptom scores took 6598 ± 4243 steps a day; those with high morning symptom scores 4727 ± 2209 steps a day (mean difference 1871, p = 0.017). Patients with high morning symptom scores took significantly fewer steps during the morning (mean difference 669, p = 0.030) and during the afternoon (mean difference 1013, p = 0.015) than patients with low morning symptom scores (Table 3). Patients with low morning symptom scores were active for longer during the afternoon (mean difference 19, p = 0.040) and spent more minutes walking during the morning (mean difference 8, p = 0.020) and afternoon (mean difference 11, p = 0.010). There were peaks in mean number of steps at 15:00 (550 steps per hour) and at 12:00 (535 steps per hour) (Figure 2). When patients with low and high morning symptom scores were categorized on medication use, there was no significant difference in mean number of steps in the morning between the groups (p = 0.057) (Supplementary materials: Figure S1). When patients were categorized on high and low mMRC score, there was a significant difference in number of steps in the morning, afternoon and evening (Supplementary materials : Figure S2).

Table 1 Baseline characteristics

Characteristic	All included patients (N = 79)	Morning symptom score <17.0 (N=41)	Morning symptom score ≥17.0 (N=38)	Difference (P-value)
Age in years, mean (SD)	65.6 (8.8)	66.4 (8.2)	64.7 (9.4)	0.38
Male, n (%)	42 (53)	25 (61)	17 (45)	0.15
Ethnicity Caucasian, n (%)	78 (99)	40 (98)	38 (100)	0.33
Current smoking, n (%)	21 (27)	8 (20)	13 (34)	0.14
Pack years, median [IQR]	37 [25-51]	34 [25-42]	41 [26-71]	0.06
In current employment, n (%)	21 (27)	12 (29)	9 (24)	0.58
BMI in kg/m^2, mean (SD)	26.4 (5.1)	25.5 (4.8)	27.3 (5.3)	0.13
FEV_1/FVC ratio, mean (SD)	45.5 (12.2)	45.6 (13.6)	45.5 (10.6)	0.99
FEV_1 % predicted, mean (SD)	55.2 (16.9)	57.2 (19.3)	53.0 (14.0)	0.28
Exacerbation in the previous year, n (%)	41 (52)	16 (39)	25 (66)	**0.017**
GOLD stage				
A, n (%)	19 (24.1)	17 (41.5)	2 (5.3)	**<0.001**
B, n (%)	22 (27.8)	9 (22.0)	13 (34.2)	0.23
C, n (%)	6 (7.6)	6 (14.6)	0 (0.0)	**0.014**
D, n (%)	32 (40.5)	9 (22.0)	23 (60.5)	**<0.001**
CCQ total score, mean (SD)	2.1 (1.1)	1.4 (0.86)	2.8 (0.9)	**<0.001**
SGRQ total score, mean (SD)	43.0 (18.6)	32.1 (16.6)	54.8 (12.4)	**<0.001**
Long-acting bronchodilation				
Use of one long-acting bronchodilator, n (%)	17 (21.5)	10 (24.4)	7 (18.4)	0.52
Use of two long-acting bronchodilators, n (%))	58 (74.7)	28 (68.3)	31 (81.6)	0.18
No long-acting bronchodilator, n (%)	3 (3.8)	3 (7.3)	0 (0.0)	0.09
CCI score, median [IQR]	2 [1-3]	2 [1-3]	2 [1-3]	0.98
History of solid tumor without metastasis, n (%)	15 (19.0)	9 (22.0)	6 (15.8)	0.49
Cerebrovascular disease, n (%)	10 (12.7)	6 (14.6)	4 (10.5)	0.58
Uncomplicated diabetes mellitus, n (%)	9 (11.4)	3 (7.3)	6 (15.8)	0.24

BMI: body mass index; CCI: Charlson comorbidity index; CCQ: clinical COPD questionnaire; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: global initiative for chronic obstructive lung disease; IQR: interquartile range; SD: standard deviation; SGRQ: St George Respiratory Questionnaire

Self-reported daily activities

Patients' median [IQR] self-reported physical activity was 715 [319;1448] minutes a week. Patients spent most of their self-reported physical activity during leisure time (Table 4). Patients with low morning symptom scores spent significantly more time in transport and

Table 2 Duration of different types of activity during the morning, afternoon, evening and night (N=79)

Activity	Total duration in mean min (SD)			
	Morning	Afternoon	Evening	Night
Active time[#]	85.5 (39.7)	112.4 (42.3)	57.2 (34.1)	8.8 (10.1)
Standing	54.9 (25.4)	67.8 (25.5)	38.7 (25.9)	6.1 (7.4)
Shuffling	8.7 (5.4)	11.6 (6.7)	5.2 (4.1)	0.8 (1.0)
Walking	22.0 (15.1)	33.0 (20.0)	13.2 (9.8)	1.9 (2.4)
Inactive time[¶]	271.6 (39.7)	246.7 (42.0)	302.0 (34.1)	351.1 (10.1)
Lying	150.6 (63.9)	42.9 (45.8)	105.7 (78.5)	327.3 (51.2)
Sitting	120.9 (44.7)	203.8 (45.6)	196.3 (72.4)	23.8 (43.3)
Not worn	2.9 (4.7)	1.0 (1.8)	0.9 (2.2)	0.2 (0.7)

SD: standard deviation. [#]: Active: standing, shuffling and walking combined; [¶]: inactive: lying and sitting combined.

leisure time activities than those with high morning symptom scores. No significant differences were found for work, housework activities and total activity.

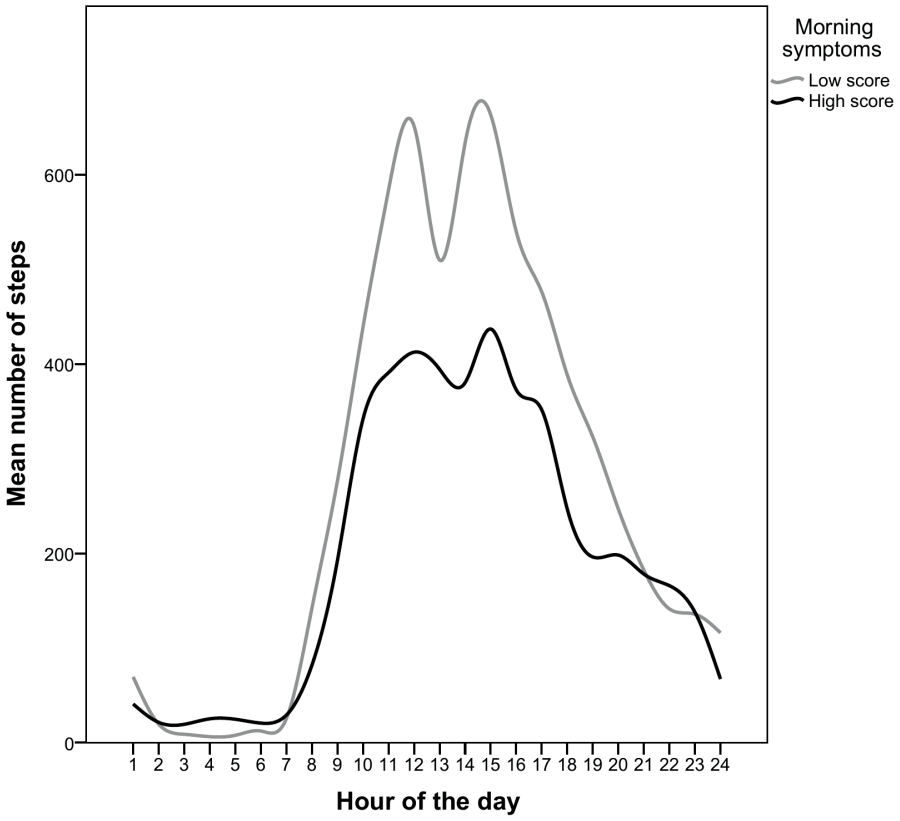

Figure 2 Steps during each hour of the day. Low morning symptom score: score <17.0; high morning symptom score: score ≥17.0.

Table 3 Differences in duration of activity during the night, morning, afternoon and evening between COPD patients with low and high morning symptom scores

		Morning symptom score <17.0 (N=41)	Morning symptoms score ≥17.0 (N=38)	P-value
Steps	Night	97 [50-173]	92 [50-138]	0.60
	Morning	2117 (1552)	1448 (1069)	**0.030**
	Afternoon	3196 (2352)	2183 (1025)	**0.015**
	Evening	1145 (858)	943 (861)	0.30
Active time (in minutes, mean (SD) or median [IQR])	Night	6 [2-11]	6 [3-10]	0.76
	Morning	91 (39)	79 (40)	0.18
	Afternoon	122 (45)	102 (38)	**0.040**
	Evening	52 [37-79]	42 [33-77]	0.19
Standing (in minutes, mean (SD) or median [IQR])	Night	3 [1;7]	4 [2;8]	0.62
	Morning	56 (24)	53 (28)	0.61
	Afternoon	71 (25)	64 (26)	0.23
	Evening	40 (24)	37 (28)	0.59
Shuffling (in minutes, mean (SD) or median [IQR])	Night	0 [0;1]	1 [0;1]	0.77
	Morning	9 (6)	8 (5)	0.33
	Afternoon	12 (7)	11 (6)	0.44
	Evening	5 [2;8]	4 [2;6]	0.32
Walking (in minutes, mean (SD) or median [IQR])	Night	13 [7-19]	9 [6-15]	0.11
	Morning	26 (17)	18 (12)	**0.020**
	Afternoon	38 (24)	27 (12)	**0.010**
	Evening	15 (10)	12 (10)	0.23
Inactive time (in minutes, mean (SD) or median [IQR])	Night	354 [349-358]	354 [350-357]	0.88
	Morning	265 (40)	278 (39)	0.14
	Afternoon	238 (44)	257 (37)	**0.043**
	Evening	299 (33)	305 (36)	0.41
Lying (in minutes, mean (SD) or median [IQR])	Night	343 [322-353]	343 [330-355]	0.89
	Morning	140 (52)	161 (74)	0.15
	Afternoon	27 [5-50]	34 [12-68]	0.14
	Evening	90 [44-138]	83 [53-151]	0.71
Sitting (in minutes, mean (SD) or median [IQR])	Night	9 [3-22]	10 [2-22]	0.74
	Morning	125 (38)	117 (51)	0.45
	Afternoon	203 (41)	205 (51)	0.85
	Evening	198 (68)	195 (78)	0.86

COPD: chronic obstructive pulmonary disease; IQR: interquartile range; SD: standard deviation.
Night N=78, morning N=78, afternoon N=79, evening N=78.

Sensitivity analysis

Seven patients reported an adverse event. One patient was exhausted due to the study visit, two patients reported pain in their hands, one had pneumonia, one had flu, one had

Table 4 Self-reported daily activities

IPAQ	Total (N=70)[#]	Morning symptom score <17.0 (N=34)	Morning symptom score ≥17.0 (N=36)	Difference (p-value)
Work, in minutes/week, median [IQR]	0 [0;0]	0 [0;30]	0 [0;0]	0.13
Transport, in minutes/week, median [IQR]	155 [11-319]	195 [53-514]	68 [0-270]	**0.047**
Housework, house maintenance and caring for family, in minutes/week, median [IQR]	120 [0-608]	105 [0-495]	150 [0-698]	0.89
Recreation, sport and leisure time in minutes/week, median [IQR]	160 [0-420]	293 [15-604]	60 [0-263]	**0.017**
Total activity minutes/week, median [IQR]	715 [219-1448]	935 [533-1808]	665 [131-1298]	0.13

IPAQ: international physical activity questionnaire; IQR: interquartile range. [#]: 9 out of 79 patients were excluded: 6 patients did not fully complete the IPAQ; 3 patients filled out unreasonably high time in physical activity (more than 960 minutes a day each day of the week).

sinusitis and one patient reported a visit to her general practitioner who prescribed a course of antibiotics and prednisone for pulmonary complaints. There were no serious adverse events. Patients with adverse events have a significant lower quality of life and reported higher morning symptom scores (Supplementary materials: Table S1). When excluding the patients with an adverse event from analyses, the cut-off on the PRO-morning COPD Symptoms Questionnaire to divide the cohort in two equal groups decreased to 15.0, since all patients with an adverse event were categorized in the high morning symptom score group. Results were nearly similar (Supplementary materials: Table S2 and S3 and Figure S3) apart from that there was no difference anymore in number of steps in the morning between patients with low and high morning symptom scores.

DISCUSSION

This study was designed to evaluate physical activity during the course of the day in patients with moderate to severe COPD with low and high morning symptom scores. This is one of the first studies that explored physical activity in more detail during the course of the day using objective methodology. We showed that patients with high morning symptom scores took significantly fewer steps in the morning and afternoon than those with low morning symptom scores. There were no differences in physical activity in the evening and night between these two groups. Patients with high morning symptom scores spent less time in transport and leisure time than patients with low morning symptom scores.

The present study showed that patients with high morning symptom scores took fewer steps during the total day. This is in line with previous studies that have shown that daily symptoms were associated with lower physical activity levels [10]. One study in a primary care setting in men who are aged between 71 and 92 years, of whom 50% had chronic conditions, [28] reported that men were most active in the morning, followed by a substantial decline in steps per hour, with peaks at times 10:00, 14:00 and 22:00. Our study showed that the afternoon is the most active part of the day for patients with COPD with peaks in steps per hour at times 12:00 and 15:00. Thus, patients with COPD have different activity patterns during the course of the day. These findings are in line with another study of activity in COPD patients; this study showed the highest activity levels during the late morning and early afternoon, followed by a decline in activity [5]. The difference in activity patterns between older men and COPD patients could possibly be explained by known activity characteristics that are typical for COPD patients: lower walking speed, [29] walking with increased duration in time between steps, [30] doing activities slower, [12] taking more breaks, [12] performing daily activities in fewer bouts [4] and shorter bouts [4].

When analysing the activity patterns in a more detailed way, the present study showed that patients with high morning symptom scores were less active during the morning and afternoon than patients with low morning symptom scores. Systematic reviews have shown that multiple determinants have impact on physical activity [31] and that morning symptoms are associated with physical activity [13]. The etiology of morning symptoms is unknown. It can be speculated that inactivity in the afternoon in patients with high morning symptom scores could be due to the long-lasting effects of morning symptoms. It could also be true that patients with morning symptoms have more symptoms during the rest of the day [32]. Interestingly, we found no difference in active time during the evening and night between patients with low and high morning symptom scores. We did not expect this, because we expected that morning symptoms would be associated with less physical activity during each part of the day as patients reported in previous studies in which physical activity was not objectively measured [15, 33]. Exploring the assumption that morning symptoms influence physical activity in the morning, but not in the evening, the evening might be a suitable part of the day in which physical activity could be enhanced, especially in those with high morning symptom scores.

In line with previous research, the present study showed that patients spent most of their self-reported physical activity in leisure time [4]. Patients with high morning symptom scores spent less time in transport and leisure time activities than patients with low morning symptom scores. Encouraging physical activity in leisure time might result in more physical activity and can also increase quality of life [34]. A few previous studies have shown that inhaled medication decreased physical activity limitations due to morning symptoms [15,

35, 36]. An explorative analysis in the present study showed no differences in physical activity between no, single or double long-acting bronchodilator use. However, this study was not powered to show differences in medication use and future research regarding this topic is warranted.

A strength of the current study was 24-h a day accelerometry. This resulted in real-life activity recording without missing physical activity during the evening and the night. However, we did not have information regarding the time patients go to bed and woke up. Consequently, patients who got out of bed early in the morning (and were already awake for a couple of hours), were compared with patients who had only just awoken. Previous studies that assessed the association between morning symptoms and physical activity used self-reported questionnaires, while accelerometers are superior in physical activity assessment than questionnaires [13, 37]. Another strength was the inclusion of patients from an academic medical center, a local hospital and patients recruited by flyers in local papers. This resulted in a heterogeneous population that is generalizable to all patients with moderate to very severe COPD. A limitation of the study was that the accelerometer was not waterproof and patients were not allowed to wear it while taking a shower. For some patients, taking a shower is one of the main physical activities during a day, and this activity was not measured. This means, active time was underestimated. A second limitation is that morning symptoms were evaluated with a non-validated questionnaire. However, there is no validated morning symptom questionnaire available yet. Patients filled in the questionnaire at the study center and not at home at the time they woke up. This might have result in recall bias that might cause higher (or lower) total morning symptom scores. The mean morning symptom score was slightly higher than in a previous study that used the PRO-Morning COPD Symptoms Questionnaire too [17]. Therefore, it could be possible that the cut-off point to separate high from low morning symptom scores was too high. However, when patients with an AE were removed and the cut-off point dropped to 15.0, the outcomes were nearly the same. Another limitation is the observational design of the study. Therefore, it is not possible to prove whether morning symptoms are fully responsible for the differences in physical activity or that physical inactivity itself resulted in more symptoms due to muscle depletion and loss of physical condition.

The ERS reported in the physical activity statement in COPD that there are only a few randomised controlled trials that studied effects of treatment on physical activity and that there is a need for additional well-designed trials [29]. Taking the outcomes of this study into account, we suggest for future research to focus on two targets to improve physical activity: first, study the etiology of morning symptoms. It would be valuable to measure night time symptoms, the effect of flow-limitation during the night (and the early morning) and the effects of spreading physical activity in relation to morning symptoms.

Improvement in morning symptoms consequently might increase the number of steps in the morning and afternoon. Second, develop activity programs that encourage physical activity in the evening in addition to daily physical activities. Physical activity programs can be supported by telecoaching and step counters that provide direct feedback [3].

CONCLUSION

This study showed that patients with moderate to very severe COPD were most active in the afternoon. Patients with high morning symptom scores took significantly fewer steps in the morning and afternoon than those with low morning symptom scores. Prospective studies are needed to prove causality between morning symptoms and physical activity during different parts of the day.

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LIST OF ABBREVIATIONS

ATS: American Thoracic Society
BMI: body mass index
CCI: Charlson Co-morbidity index
CCQ: clinical COPD questionnaire
COPD: Chronic obstructive pulmonary disease
ERS: European Respiratory Society
FEV1: Forced expiratory volume in 1 second
FVC: forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
IPAQ: international physical activity questionnaire
IQR: interquartile ranges
LABA: long-acting beta2 agonist
LAMA: long-acting muscarinic antagonist
LUMC: Leiden University Medical Center
mMRC: modified medical research council
MODAS: Morning symptoms in-Depth observAtional Study
SD: standard deviation
SGRQ: St George's Respiratory Questionnaire

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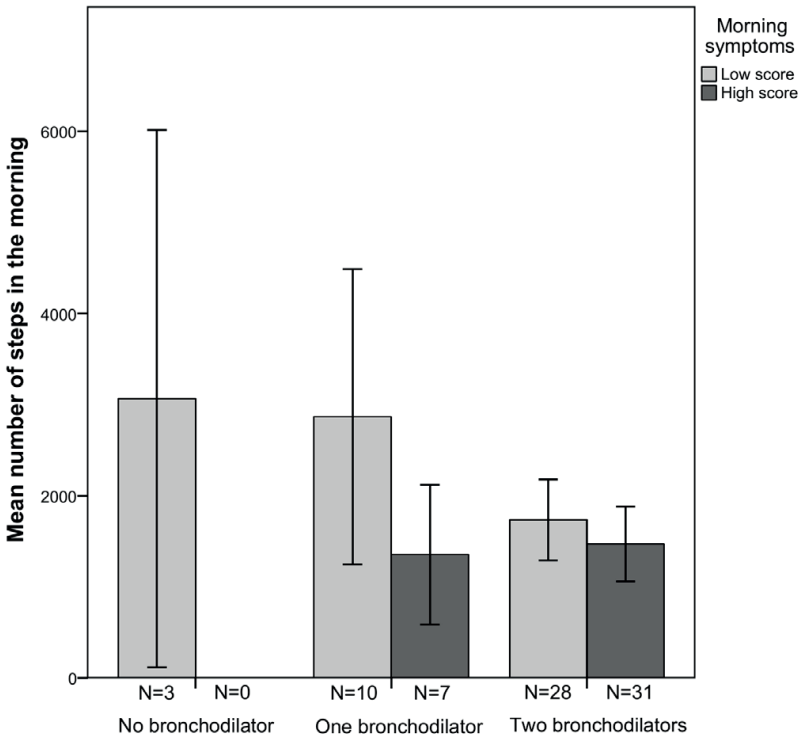
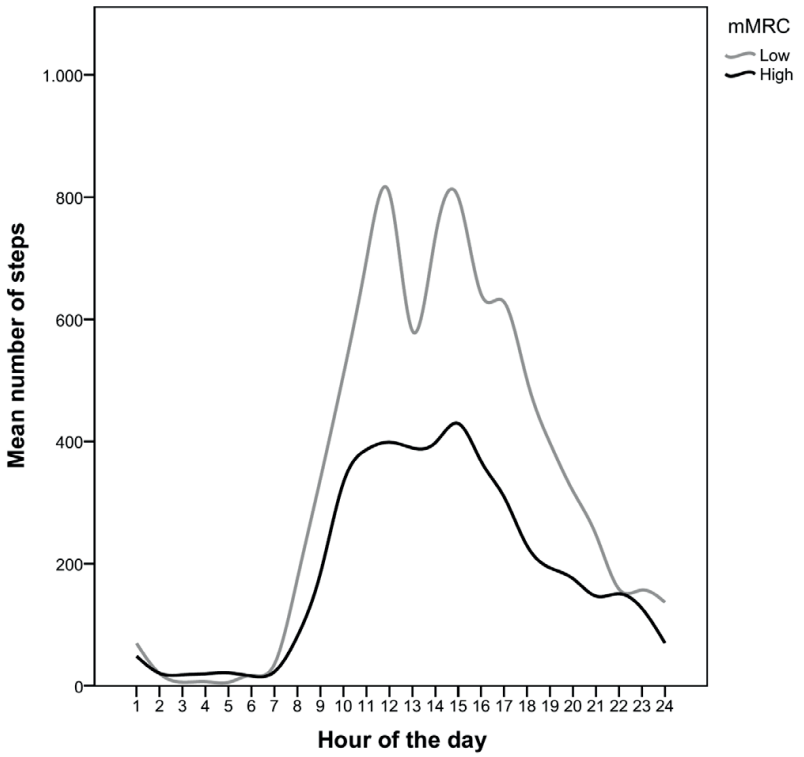
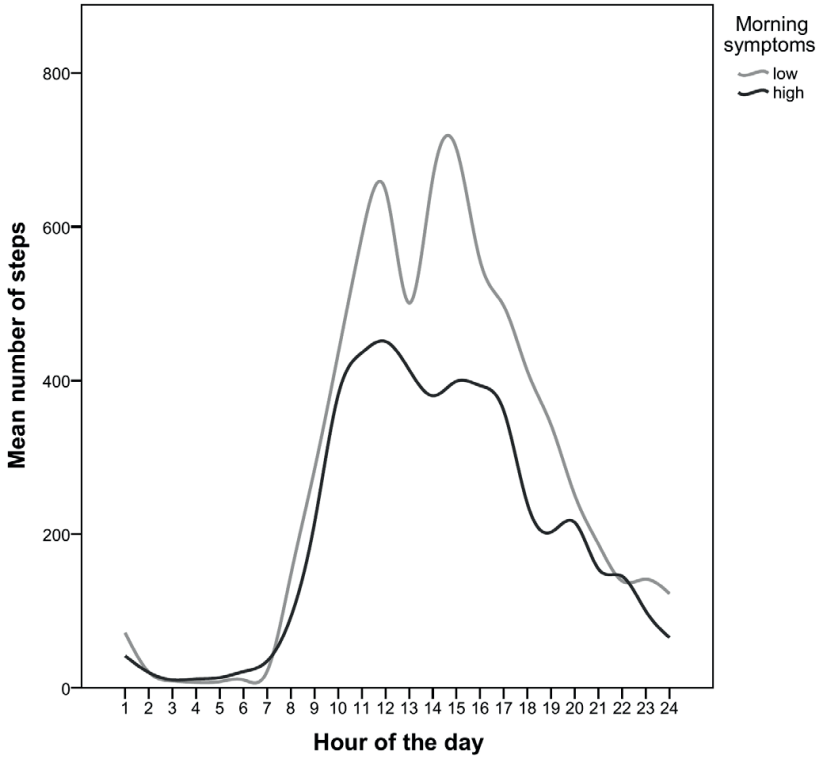
SUPPLEMENTARY MATERIALS



Supplementary figure 1. Number of steps in the morning. Error bare present 95% confidence intervals. Low morning symptom score: score <17.0; high morning symptom score: score ≥17.0.



Supplementary figure 2. Steps during each hour of the day. Low mMRC <2 (N=27); high mMRC ≥2 (N=52).



Supplementary figure 3. Steps during the course of the day. Low morning symptom score <15.0; high morning symptom score ≥15.0

Supplementary table 1 Baseline characteristics for patients with and without an adverse event

Characteristic	All included patients (N = 79)	With AE (N=7)	Without AE (N=72)	Difference (p-value)
Age in years, mean (SD)	65.6 (8.8)	69.4 (7.2)	65.2 (8.9)	0.23
Male, n (%)	42 (53)	4 (57)	38 (53)	0.83
Ethnicity Caucasian, n (%)	78 (99)	7 (100)	71 (99)	0.75
Current smoking, n (%)	21 (27)	1 (14)	20 (28)	0.44
Pack years, mean (SD)	37 [25-51]	51 [30-110]	35 [25-50]	0.10
In current employment, n (%)	21 (27)	0 (0)	21 (29)	0.10
BMI in kg/m^2, mean (SD)	26.4 (5.1)	30.5 (8.6)	26.0 (4.5)	0.22
FEV1/FVC ratio, mean (SD)	45.5 (12.2)	47.9 (6.6)	45.3 (12.6)	0.60
FEV$_1$ % predicted, mean (SD)	55.2 (16.9)	60.6 (9.5)	54.6 (17.5)	0.38
Exacerbation in the previous year, n (%)	41 (52)	6 (85.7)	35 (48.6)	**0.06**
GOLD stage				
A, n (%)	19 (24.1)	0 (0.0)	19 (26.4)	0.12
B, n (%)	22 (27.8)	2 (28.6)	20 (27.8)	0.96
C, n (%)	6 (7.6)	0 (0.0)	6 (8.3)	0.43
D, n (%)	32 (40.5)	5 (71.4)	27 (37.5)	0.08
CCQ total score, mean (SD)	2.1 (1.1)	3.0 (0.7)	2.0 (1.1)	**0.029**
SGRQ total score, mean (SD)	43.0 (18.6)	59.1 (11.5)	41.4 (18.4)	**0.015**
Long-acting bronchodilation				
Use of one long-acting bronchodilator, n (%)	17 (21.5)	1 (14.3)	16 (22.2)	0.63
Use of two long-acting bronchodilators, n (%))	59 (74.7)	6 (85.7)	53 (73.6)	0.48
No long-acting bronchodilator, n (%)	3 (3.9)	0 (0.0)	3 (4.2)	0.58
CCI score, median [IQR]	2 [1;3]	2 [1;2]	2 [1;3]	0.91
History of solid tumor without metastasis, n (%)	15 (19.0)	0 (0.0)	15 (20.8)	0.18
Cerebrovascular disease, n (%)	10 (12.7)	0 (0.0)	10 (13.9)	0.29
Uncomplicated diabetes mellitus, n (%)	9 (11.4)	3 (42.9)	6 (8.3)	**0.006**
Morning symptom score, mean (SD)	17.9 (11.8)	29.3 (5.7)	16.8 (11.7)	**<0.001**

AE: adverse event; BMI: body mass index; CCQ: clinical COPD questionnaire; CCI: Charlson co-morbidity index; FEV$_1$: Forced expiratory volume in 1 second; FVC: forced vital capacity; IQR: interquartile range; SD: standard deviation, SGRQ: St George Respiratory Questionnaire

Supplementary table 2 Differences in activity during the night, morning, afternoon and evening between patient with low and high morning symptom scores, N=72

		Few morning symptoms (score <15)	Severe morning symptoms (score ≥15)	Difference (p-value)
Steps	Night	89 [50;181]	91 [41;143]	0.47
	Morning	2122 (1624)	1609 (1071)	0.12
	Afternoon	3309 (2449)	2186 (990)	**0.013**
	Evening	1182 (893)	883 (652)	0.11
Active time (in minutes, mean (SD) or median [IQR])	Night	6 [2;11]	5 [3;11]	0.85
	Morning	92 (39)	85 (39)	0.44
	Afternoon	125 (45)	103 (37)	**0.023**
	Evening	55 [34;80]	46 [33;76]	0.21
Standing (in minutes, mean (SD) or median [IQR])	Night	3 [1;8]	3 [2;7]	0.66
	Morning	57 (23)	57 (28)	0.97
	Afternoon	72 (24)	65 (26)	0.21
	Evening	42 (25)	39 (29)	0.63
Shuffling (in minutes, mean (SD) or median [IQR])	Night	0 [0;1]	0 [0;1]	0.80
	Morning	9 (6)	8 (5)	0.37
	Afternoon	13 (7)	10 (5)	0.11
	Evening	5 [2;8]	4 [2;6]	0.31
Walking (in minutes, mean (SD) or median [IQR])	Night	13 [7;20]	10 [6;15]	0.15
	Morning	26 (17)	20 (12)	0.11
	Afternoon	40 (25)	27 (11)	**0.008**
	Evening	15 (10)	11 (8)	0.11
Inactive time (in minutes, mean (SD) or median [IQR])	Night	354 [349;358]	354 [349;357]	0.88
	Morning	264 (40)	273 (38)	0.36
	Afternoon	234 (45)	256 (37)	**0.023**
	Evening	297 (34)	304 (36)	0.40
Lying (in minutes, mean (SD) or median [IQR])	Night	343 [317;353]	342 [331;355]	0.75
	Morning	140 (53)	154 (68)	0.31
	Afternoon	27 [7;48]	44 [12;84]	0.08
	Evening	79 [43;134]	100 [51;196]	0.35
Sitting (in minutes, mean (SD) or median [IQR])	Night	9 [3;31]	10 [2;16]	0.54
	Morning	125 (40)	119 (46)	0.56
	Afternoon	200 (40)	200 (49)	0.95
	Evening	200 (66)	187 (81)	0.45

Night N=71, morning N=71, afternoon N=72, evening N=71. IQR: interquartile range; SD: standard deviation.

Supplementary table 3 Daily physical activity

IPAQ	Total (N=64)*	A few morning symptoms (N=31)	Severe morning symptoms (N=33)	Difference (p-value)
Work, in minutes/week, median [IQR]	0 [0;0]	0 [0;30]	0 [0;0]	0.31
Transport, in minutes/week, median [IQR]	155 [5;326]	210 [30;525]	60 [0;240]	**0.015**
Housework, house maintenance and caring for family, in minutes/week, median [IQR]	120 [0;653]	180 [0;540]	120 [0;780]	0.67
Recreation, sport and leisure time in minutes/week, median [IQR]	180 [0;465]	345 [20;615]	60 [0;285]	**0.035**
Total activity minutes/week, median [IQR]	815 [338;1478]	990 [600;1920]	540 [90;1285]	**0.047**

IPAQ: international physical activity questionnaire; IQR: interquartile range. *5 patients did not fully complete the IPAQ; 3 patients filled out unreasonably high time in physical activity (more than 960 minutes a day each day of the week).

Pulmonary function and medication use are associated with physical activity in very mild to moderate COPD: a population based study

Authors

Amanda R. van Buul[1]
Marise J. Kasteleyn[1,2]
Raoul G.A.J.M. Helmes[2]
Tobias N. Bonten[1,2]
Renée de Mutsert[3]
Pieter S. Hiemstra[1]
Saskia le Cessie[3,4]
Frits R. Rosendaal[3,5]
Niels H. Chavannes[2]
Christian Taube[1,6]

Affiliations

[1]Dept of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands.
[2]Dept of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands.
[3]Dept of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.
[4]Dept of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands
[5]Dept of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands
[6]Dept of Pulmonary Medicine, West German Lung Center, Essen University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany

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ABSTRACT

Background: Physical inactivity is a characteristic of chronic obstructive pulmonary disease (COPD) and has so far especially been studied in more advanced COPD. Yet, inconsistent findings were reported about determinants of physical activity including COPD treatment. Further understanding of physical activity in non-severe COPD could lead to interventions that increase physical activity. Therefore, the aim of this study was to explore patient characteristics that are related with physical activity in COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0-2.

Methods: The study presents a cross-sectional analysis of baseline data of patients with physician diagnosed (N=77) and newly diagnosed (N=246) COPD GOLD 0-2 that were selected from the population-based Netherlands Epidemiology of Obesity study. Physical activity was reported using the Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH) questionnaire and reported in hours per week of metabolic equivalents (MET-h/week). Associations between characteristics and physical activity were examined using regression analysis, adjusted for age and gender and weighted for body mass index.

Results: Weighted median [IQR] reported physical activity was 31 [15-46] MET-h/week. In newly diagnosed patients, forced expiratory volume in one second (FEV_1) (0.4 MET-h/week per percent FEV_1, 95%CI 0.1,0.8) and forced vital capacity (FVC) (0.4 MET-h/week per percent FVC, 95%CI 0.1,0.7) were positively associated with physical activity. The presence of long-acting muscarinic antagonists (LAMA) and a combination of inhaled corticosteroids (ICS)/long-acting beta2 agonists(LABA)/LAMA were associated with less physical activity in newly diagnosed COPD.

Conclusions: Intervention studies are needed to determine whether early pharmacological interventions and/or physical activity slow down COPD progression in non-severe COPD.

Keywords: General population, physical activity, chronic obstructive pulmonary disease, pulmonary function

BACKGROUND

Physical inactivity is a common worldwide problem and is especially observed in patients with chronic diseases such as chronic obstructive pulmonary disease (COPD).[1] Only 26% to 30% of patients with COPD were reported to fulfil the World Health Organisation physical activity recommendations compared to 54% among apparently healthy adults.[1] Inactivity in COPD is associated with more hospitalizations and mortality.[2] The European Respiratory Society statement of physical activity in COPD recommends sufficient physical activity in COPD.[3] However, it is incompletely understood why patients with COPD are inactive. One possibility is that patients are inactive because they try to avoid worsening of COPD symptoms. Increased symptoms and dynamic hyperinflation during exercise can be observed in patients with mild COPD.[4] The decline in physical activity already starts in mild disease stages, even before the physician diagnosis of COPD is made.[5-8]

Defining patient characteristics that are associated with physical inactivity is important for the development of targeted interventions. Multiple characteristics have been reported to be related to physical activity in COPD[3], but the role of most characteristics is unclear and inconsistent findings have been reported.[9] Dyspnoea, quality of life and previous exacerbations are consistently associated with physical inactivity in COPD.[9] However, these characteristics together do not fully explain the lack of physical activity in COPD. In addition, in most previous studies regarding physical activity, only half of patients were non-severe COPD patients,[6, 8, 10-13] or the mean forced expiratory volume in one second (FEV_1) was lower than 50%.[14-20] Studies that included only non-severe COPD are sparse.[5, 7] However, especially in this patient population there appears to be most room for improvement. Therefore, better knowledge of the characteristics that are related with physical activity in COPD Global Initiative for Chronic Obstructive Lung Diseases (GOLD) 0, 1 and 2 patients is needed. The aim of the present study was to explore physical activity and patient characteristics that were associated with physical activity in patients with COPD GOLD 0, 1 and 2. The focus was on patient characteristics of which inconsistent effects were described in previous studies.

METHODS

Study design

Cross-sectional analyses of baseline data from the Netherlands Epidemiology of Obesity (NEO) study are presented. The NEO study is a population-based prospective cohort study, with an oversampling of individuals with a body mass index (BMI) of 27kg/m^2. From 2008 to 2012 6,671 participants were included in the NEO study. The study design and popula-

tion are described in detail elsewhere.[21] Briefly, men and women, aged between 45 and 65 years with a self-reported BMI of 27kg/m^2 or higher, living in the greater area of Leiden, the Netherlands, were invited to participate. In addition, all inhabitants aged between 45 and 65 years in one municipality (Leiderdorp, the Netherlands) were invited irrespective of their BMI, allowing for a reference distribution of BMI. The Medical Ethical Committee of the Leiden University Medical Center approved the study design. All participants gave their written informed consent.

Participants were invited to a baseline visit at the NEO study center of the Leiden University Medical Center. Prior to this study visit, participants completed questionnaires at home, including a physical activity questionnaire. During the study visit a physical examination was performed, height and weight were measured and BMI was calculated. During this visit pulmonary function tests were performed at the Department of Pulmonology at the Leiden University Medical Center. Fractional nitric oxide (Fe_{NO}) was measured with a Niox Mino (Aerocrine AB, Solna, Sweden). In 2013, medical history, International Classification of Primary Care (ICPC) codes and medication prescription were obtained through the electronic medical record registry of the general practitioners.

Study population

For the present study, participants were included if they had physician diagnosed COPD with an ICPC code for COPD (R95). Since COPD is often underdiagnosed,[22] we also included patients who did not have physician diagnosed COPD, but met our definition of newly diagnosed COPD. Newly diagnosed COPD was defined as an obstructive lung function with a FEV_1/forced vital capacity (FVC) <0.7 and not having a combination of a smoking history less than 20 pack-years and no pulmonary symptoms.[23] Pulmonary symptoms included dyspnoea, wheezing, cough, sputum production or other pulmonary symptoms that could be reported on the questionnaire. Participants were excluded if the FEV_1 was lower than 50%, since the focus of this study was on non-severe COPD. Furthermore, participants were excluded if they had a diagnosis of asthma (defined as ICPC code R96) and/or were never smokers and/or had a Fe_{NO} concentration in exhaled breath of ≥25 parts per billion, since these outcomes are more suggestive for asthma than for COPD. Participants with missing data on the key variables were excluded.

Data collection

Participants in the NEO study reported their usual weekly physical activity during the preceding four weeks with the validated Short Questionnaire to Assess Health-enhancing physical activity (SQUASH).[24] Participants reported the frequency and duration of their physical activity in leisure time which was expressed in hours per week of metabolic equivalents (MET-h/week).

A large number of characteristics might be associated with physical activity.[9] We examined three clusters of characteristics that were previously used in a systematic review.[9] These clusters were: *sociodemographic and lifestyle characteristics*; *clinical and functional characteristics* and *pharmacological characteristics*. The characteristics of which inconsistent findings were reported in previous studies, were collected. For *sociodemographic and lifestyle characteristics* participants reported age, sex, pack-years, alcohol consumption, ethnicity education level, working status and smoking status. Ethnicity was grouped into white (reference) and other; education level into high and low (reference); working status into working and not working (reference), smoking status into current and former (reference). For *clinical and functional characteristics* information was collected regarding pulmonary symptoms, presence of a physician diagnosed COPD, anxiety, depression, BMI, FEV_1 and FVC. Pulmonary symptoms included dyspnoea, wheezing, cough, sputum production or other pulmonary symptoms that could be reported on the questionnaire. Participants reported symptoms or no symptoms (reference). They reported on the questionnaire whether they experienced an increase in symptoms in the morning or no increase (reference). Anxiety and depression were examined with the Beck Anxiety Inventory (BAI) [25] and the Inventory of Depressive Symptomatology (IDS) questionnaire[26] respectively. Lung function was assessed by spirometry (Jaeger Masterscreen PFT; Viasys Healthcare, Hoechberg, Germany), that was performed according to the standards of the European Respiratory Society.[27] FEV_1 and FVC were reported as percentage predicted normal based on sex, age and height. For *pharmacological characteristics* information was collected regarding pulmonary medication use. The following medications could be recorded: all short-acting medication, all long-acting medication, short-acting beta2 agonists (SABA), short-acting muscarinic antagonists (SAMA), inhaled corticosteroids (ICS), long-acting beta2 agonists (LABA), long-acting muscarinic antagonists (LAMA) or a combination of long-acting pulmonary medication: ICS/LABA or ICS/LABA/LAMA. No use of pulmonary medication was used as reference.

Statistical analysis

Descriptive data of baseline characteristics were reported as percentages, mean and standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) when not normally distributed.

Patients were classified according to the GOLD 2011 statement: those with a FEV_1/FVC $\geq$0.7 were classified as COPD GOLD 0, those with a FEV_1/FVC <0.7 and a FEV_1 $\geq$80% predicted as GOLD 1, and those with a FEV_1/FVC <0.7 and a FEV_1 50-80% predicted as GOLD 2. Additionally, the patient group was divided in physician diagnosed (ICPC code R95 present) and newly diagnosed COPD (no ICPC code R95, but met the afore mentioned criteria for newly diagnosed COPD). For each GOLD stage, the median MET-h/week and the

presence of pulmonary symptoms were calculated. Differences in MET-h/week between the grades were examined by regression analysis.

Univariate regression analysis was used to evaluate the association between characteristics and physical activity for physician diagnosed COPD and newly diagnosed COPD separately. To investigate whether the association between determinants and physical activity was similar across the physician diagnosed group and the newly diagnosed group, the interactions between each determinant and the group indicator (ICPC R95 present or not) were tested by fitting multiple linear regression models on both groups together. These models included the determinant and the group indicator, and the interaction between the determinant and group indicator. Also the covariates age and sex were included. When the interaction was not statistically significant (p value for heterogeneity >0.10), an overall estimated of the association between the determinant and physical activity was obtained. In the cluster *sociodemographic and lifestyle characteristics* the association of physical activity with education level, working, smoking and alcohol intake was examined; in the cluster *clinical and functional characteristics* the association between pulmonary symptoms, increase of symptoms in the morning, BMI, anxiety/depression, FEV_1, FVC, a physician diagnosed COPD and physical activity was examined; in the cluster *pharmacological characteristics* the association between the use of pulmonary medication, short-acting pulmonary medication, long-acting pulmonary medication, ICS, LABA, LAMA or use of a combination and physical activity was examined. Since age and sex are associated with physical activity in healthy older people, as well as in COPD patients,[9, 28] analyses were adjusted for age and sex. We did not adjust for other characteristics, since age and sex were the only characteristics of which consistent results were found in previous studies. [9] In view of the non-normal distribution of physical activity, regression coefficients and robust standard errors were used to calculate 95% confidence intervals.

All results were weighted to represent a general population with a normal BMI distribution.[29] This was done by weighting the participants towards the BMI distribution of participants from the Leiderdorp municipality, whose BMI distribution was similar to the BMI distribution of the general Dutch population. Consequently, the results apply to a population-based study without oversampling of participants with a BMI ≥27 kg/m2. Statistical analysis was performed using Stata Statistical Software version 14.1. (StataCorp, College Station, TX, USA).

RESULTS

From the 6,671 participants in the NEO database, 323 participants (4.8% of the total cohort) fulfilled the study criteria (Figure 1). Table 1 shows the baseline characteristics. 77 patients had physician diagnosed COPD and 246 patients had newly diagnosed COPD. Those with physician diagnosed COPD were more frequently women, had a lower FEV_1, were less physically active, and used more frequently pulmonary medication than those with newly diagnosed COPD. The majority (55.4%) of participants met the criteria for newly diagnosed COPD GOLD 1.

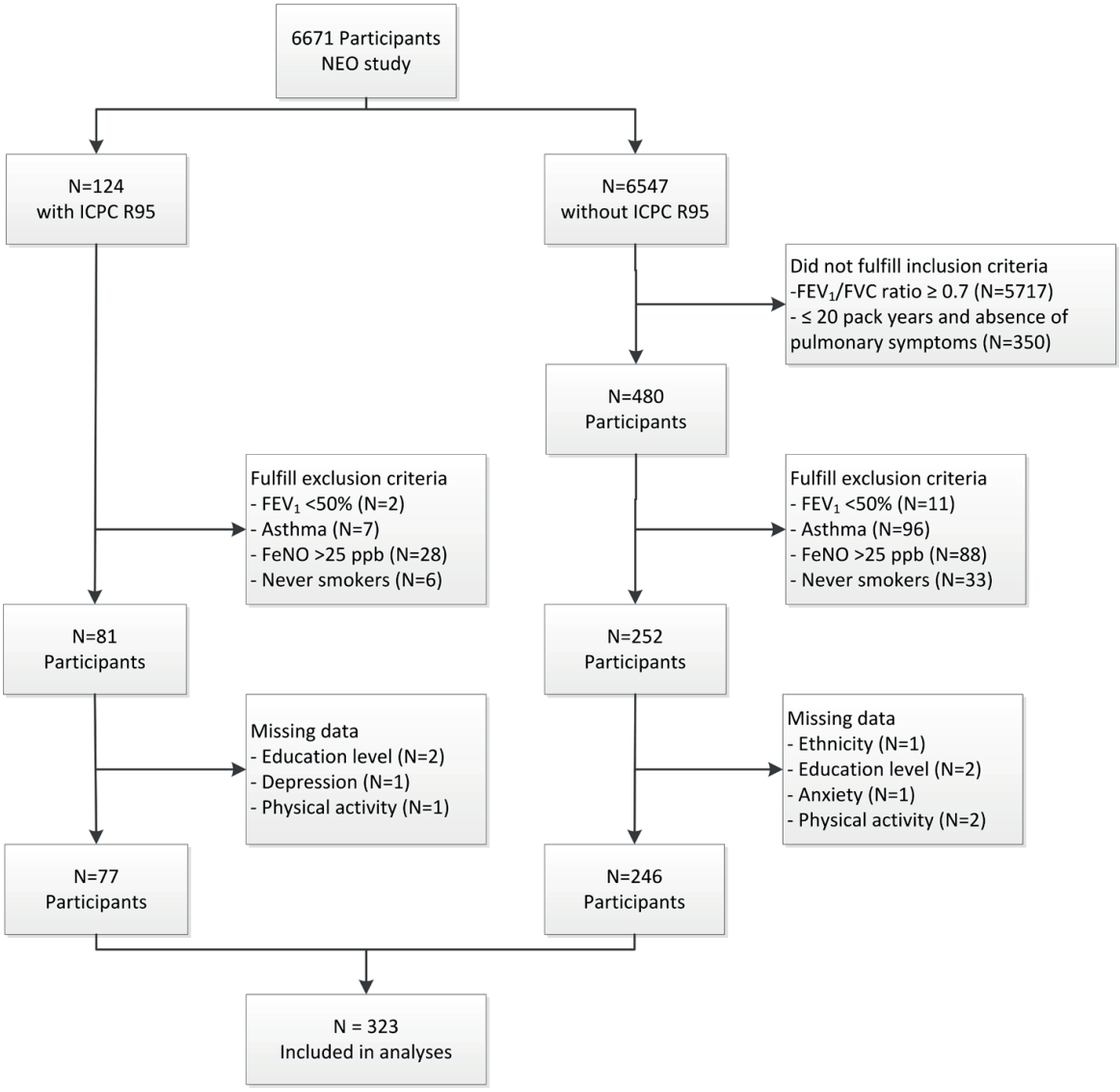

Figure 1 Flow chart of study design

COPD: chronic obstructive pulmonary disease; Fe_{NO}: fractional exhaled nitric oxide; FEV_1: Forced expiratory volume in one second; FVC: forced vital capacity; NEO: Netherlands Epidemiology of Obesity

Table 1. Characteristics of patients with physician diagnosed COPD (GOLD 0-2) and newly diagnosed COPD (GOLD 1-2)

Characteristics	Physician diagnosed (N=77)	Newly diagnosed (N=246)
Sociodemographic and lifestyle characteristics		
Age (years), median [IQR]	59 [54-64]	60 [54-63]
Sex (% female)	64	40
Education level (% high)	23	36
Working status (% working)	51	54
Smoking status (% current)	47	51
Alcohol intake (g/d), median [IQR]	15 [0-28]	21 [7-35]
Clinical and functional characteristics		
BMI (kg/m^2), mean (SD)	28 (5)	27 (4)
Anxiety (score), median [IQR]	4 [1-8]	3 [1-6]
Depression (score), median [IQR]	7 [6-17]	8 [5-13]
FEV_1 (% predicted), mean (SD)	82 (16)	90 (15)
FVC (% predicted), mean (SD)	108 (17)	112 (16)
Pulmonary symptoms (% yes)	64.8	56.8
Morning symptoms (% yes)	7	18
Physical activity in leisure time (MET hours per week), median [IQR]	20 [11-32]	33 [20-55]
Pharmacological characteristics		
Any pulmonary medication (% yes)	63.6	9.2
Short acting (% yes)	19.1	1.9
Long acting (% yes)	60.2	4.9
ICS (% yes)	46.3	4.8
LABA (% yes)	37.5	3.3
LAMA (% yes)	30.8	0.5
ICS/LABA (% yes)	14.5	3.0
ICS/LABA/LAMA (% yes)	19.1	0.3

BMI: body mass index; CI: confidence interval; COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: global initiative for chronic obstructive lung disease; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist

Patients without a physician diagnosed COPD and a FEV_1/FVC ≥0.7 were excluded; therefore, no patients were classified as newly diagnosed COPD GOLD 0. Participants reported a median [IQR] of 31 [15-46] MET-h/week in physical activity. Patients with physician diagnosed GOLD 0, 1 and 2 reported a median [IQR] of 26 [23;32], 14 [11;32] and 12 [6;32] MET-h/week in physical activity, respectively. Newly diagnosed GOLD 1 and 2 35 [22;59] and 29 [16;36] MET-h/week (Figure 2). Supplementary table 1 shows that in each group approximately half of the patients reported lung symptoms.

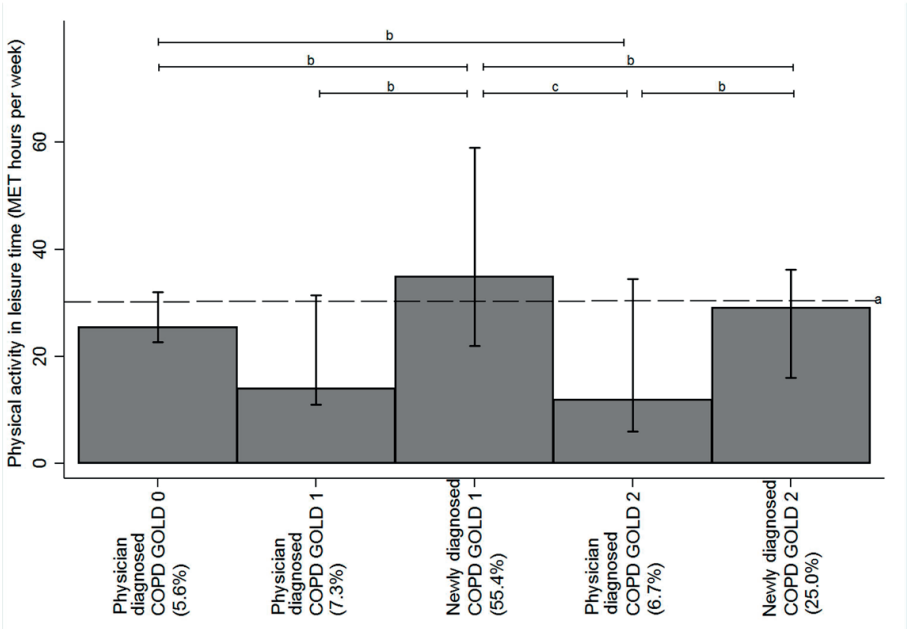

Figure 2 Physical activity in physician diagnosed and newly diagnosed COPD GOLD 0, 1 and 2
COPD: Chronic obstructive pulmonary disease; GOLD: global initiative for chronic obstructive lung disease; MET: metabolic equivalent task; NEO: Netherlands Epidemiology of Obesity
Bar plots represent the medians and error bars the interquartile range.
[a]Median MET-h/week in leisure time physical activity in the complete case NEO cohort (N=6,100)
[b]p<0.05
[c]p<0.001

Table 2 shows associated characteristics of physical activity. The characteristics education, BMI, anxiety, depression, FEV_1, FVC, LAMA and ICS/LABA/LAMA showed a statistically significant heterogeneity (p<0.1) across physician diagnosed and newly diagnosed patients. In both groups, education, BMI and depression were not associated with physical activity. Anxiety was positively associated with physical activity in physician diagnosed patients. The regression coefficient was 0.9 (95% CI 0.3,1.6) MET-h/week, representing an increase in physical activity of 0.9 MET-h/week per point increase on the BAI. This association was not statistically significant in newly diagnosed patients. Statically significant positive associations between both FEV_1 and FVC and physical activity were found in newly diagnosed patients, but not in physician diagnosed patients. The regression coefficients were 0.4 (95% CI 0.1,0.7) and 0.34 (95% CI 0.1,0.6). This indicates an increase of 0.4 MET-h/week per percent FEV_1 and an increase of 0.3 MET-h/week per percent FVC. In the newly diagnosed COPD group, but not in physician diagnosed patients, there was negative association between LAMA and ICS/LABA/LAMA use and physical activity (Table 2).

For the determinants that showed no significant heterogeneity, we found a negative association between working status and physical activity in the physician diagnosed group and a negative association between long acting therapy and physical activity in the total group (Table 2).

Table 2. Associated characteristics of physical activity in patients with physician diagnosed COPD (GOLD 0-2)

	Physician diagnosed (n = 77)		Physician diagnosed (n = 77)		Newly diagnosed (n = 246)	
Characteristics	**Unadjusted leisure time physical activity (MET-h/week)**		**Adjusted* leisure time physical activity (MET-h/week)**		**Unadjusted leisure time physical activity (MET-h/week)**	
	Regression coefficient	**95% CI**	**Regression coefficient**	**95% CI**	**Regression coefficient**	**95% CI**
Sociodemographic and lifestyle characteristics						
Education level (ref low)	6.7	-4.3;17.6	4.5	-6.4;15.4	-9.9	-20.8;0.9
Working status (ref not working)	-11.1	-18.9;-3.3	-10.1	**-18.6;-1.5**	-9.0	-21.4;3.4
Smoking status (ref former)	-3.1	-12.2;6.0	-0.1	-9.7;9.5	-3.2	-15.7;9.2
Alcohol intake (g/d)	0.1	-0.1;0.3	0.0	-0.2;0.2	0.2	-0.3;0.7
Clinical and functional characteristics						
BMI (kg/m^2)	0.4	-0.3;1.0	0.4	-0.3;1.1	-1.2	-2.9;0.4
Anxiety (score)	0.7	-0.1;1.5	0.9	**0.3;1.6**	-0.4	-1.2;0.4
Depression (score)	0.3	-0.3;0.8	0.4	-0.0;0.9	-0.3	-1.0;0.4
Worsening of symptoms in the morning (ref no worsening)	-8.8	-20.0;2.4	-6.5	-18.9;5.9	10.9	-16.9;38.6
FEV_1 (% predicted)	0.0	-0.3;0.3	-0.0	-0.3;0.3	0.5	0.1;0.8
FVC (% predicted)	-0.2	-0.4;0.1	-0.2	-0.5;0.1	0.4	0.1;0.7
Pulmonary symptoms (ref no)	1.5	-7.4;10.5	3.6	-6.4;13.6	1.2	-10.7;13.0
Pharmacological characteristics						
Any pulmonary medication (ref no)	-6.0	-13.9;2.0	-6.0	-13.5;1.5	-4.0	-17.1;9.1
Short acting therapy (ref no)	-1.3	-12.2;9.6	-1.2	-12.8;10.5	18.5	-20.4;57.4
Long acting therapy (ref no)	-6.8	-14.6;1.1	-6.8	-14.2;0.6	-4.6	-15.0;5.9
ICS (ref no)	-2.1	-11.4;7.2	-4.0	-12.4;4.5	-4.2	-14.7;6.3
LABA (ref no)	2.0	-8.2;12.1	1.0	-8.7;10.7	-2.3	-14.1;9.5
LAMA (ref no)	-8.0	-16.0;0.1	-7.2	-15.6;1.1	-21.7	-30.8;-12.5
ICS/LABA (ref no)	8.9	-8.0;25.8	8.6	-6.2;23.4	0.0	-11.2;11.2
ICS/LABA/LAMA (ref no)	-3.7	-13.8;6.3	-4.8	-15.9;6.2	-24.7	-33.8;-15.6

Results were based on analyses weighted towards the BMI distribution of the general population
BMI: body mass index; CI: confidence interval; COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: global initiative for chronic obstructive lung disease; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; MET: Metabolic Equivalent Task. *Adjusted for age and sex. $^{\$}$Models include determinant and group. $^{\#}$Models include determinant, group, age, sex.

Newly diagnosed (n = 246)			All patients (n=323)		All patients (n=323)	
Adjusted* leisure time physical activity (MET-h/week)			Unadjusted Pooled estimate[$]		Adjusted Pooled estimate[#]	
Regression coefficient	95% CI	P value * (heterogeneity)	Regression coefficient	95% CI	Regression coefficient	95% CI
-10.7	-21.6;0.24	0.088	-	-	-	-
-5.7	-23.5;12.2	0.735	-9.4	-19.4-0.7	-6.7	-20.5;7.0
-3.6	-15.5;8.3	0.462	-3.2	-13.4;6.9	-2.6	-12.8;7.7
0.2	-0.3;0.6	0.467	0.2	-0.2;0.6	0.1	-0.2;0.5
-1.1	-2.6;0.5	0.098	-	-	-	-
-0.3	-1.1;0.6	0.016	-	-	-	-
-0.3	-0.9;0.4	0.097	-	-	-	-
10.4	-15.0;35.9	0.263	8.8	-16.2;33.8	8.9	-14.5;32.3
0.4	**0.1;0.8**	0.056	-	-	-	-
0.4	**0.1;0.7**	0.002	-	-	-	-
1.2	-10.1;12.6	0.673	1.2	-8.5;11.0	1.8	-7.9;11.4
-4.1	-17.4;9.2	0.798	-4.8	-13.3;3.7	-4.9	-13.4;3.7
21.0	-17.9;60.0	0.295	5.2	-11.9;22.2	6.1	-11.9;24.2
-6.0	-16.2;4.3	0.872	-5.8	-12.3;0.7	-6.4	**-12.5;-0.2**
-5.4	-15.5;4.7	0.930	-3.0	-9.8;3.8	-5.0	-11.9;2.0
-5.6	-18.3;7.2	0.463	0.4	-7.0;7.9	-1.7	-9.4;6.0
-27.9	**-40.5;-15.3**	0.009	-	-	-	-
-2.9	-14.8;9.1	0.293	4.5	-5.5;14.5	2.1	-7.8;12.1
-31.0	**-42.7;-19.2**	0.001	-	-	-	-

DISCUSSION

The aim of the present study was to explore physical activity and associated characteristics of physical activity in patients with very mild to moderate COPD (GOLD 0, 1 and 2). The focus was on patient characteristics of which inconsistent effects were described in previous studies. The main conclusion is that several characteristics were associated with physical activity. In the total group, long acting therapy was negatively associated with physical activity. Whereas pulmonary function and anxiety were positively associated with physical activity in newly diagnosed and physician diagnosed respectively, the use of LAMA and ICS/LABA/LAMA combination therapy were negatively associated with physical activity in physician diagnosed COPD. Working status was negatively associated with physical activity in physician diagnosed COPD. We found no association of physical activity with education level, smoking status, alcohol intake, BMI, depression, pulmonary symptoms or morning symptoms.

In the present study, patients reported a median [IQR] of 31 [15-46] MET-h/week in physical activity. A study in patients with non-severe COPD that used accelerometry to evaluate physical activity, has previously reported lower physical activity.[7] Other studies that included COPD patients with mild and moderate COPD, but also patients (very) severe COPD, reported physical activity of the total study group and did not make a distinction in physical activity between severe and non-severe COPD patients which makes it difficult to compare the results with those of the present study.

In newly diagnosed patients FEV_1 was associated with physical activity which is in line with some,[10, 15, 16, 30, 31] but not all[14, 17] previous studies in patients with COPD. Per decrease of percent FEV_1, patients spent 0.4 MET-h/week less time in leisure time physical activity. This outcome is a likely relevant number of MET-h/week in COPD, since the effect of intensive exercise training in COPD is only five minutes more walking a day (which is equivalent to 1.75 MET-h/week).[32] The severity of the consequences of mild airflow limitation should not be underestimated. Patients with mild COPD have objectively measured greater ventilatory inefficiency than controls,[4, 33] which might explain the lower physical activity. This is supported by another study in newly diagnosed COPD patients, showing that a lower diffusion capacity was associated with lower physical activity.[7] Intervention studies are needed to determine whether early pharmacological interventions and/or physical activity slow down COPD progression in non-severe COPD.

LAMA and ICS/LABA/LAMA use were associated with less physical activity in this study in newly diagnosed patients, whereas ICS, LABA and ICS/LABA use were not associated with physical activity. Two cross-sectional studies have shown no differences in beta2-

agonists, anticholinergics or ICS use in moderate to very severe COPD patients or patients post-exacerbation between those with low, moderate and high physical activity.[14, 15] However, in those studies nearly all patients were using medication which makes the probability of finding a difference low. It is not likely that the use of pulmonary medication contributed to lower physical activity since placebo-controlled trials have shown positive effects of a LABA[34, 35] or a LAMA/LABA combination on physical activity.[36]. The most likely explanation is that patients with pulmonary medication have more severe COPD or experience more severe symptoms that result in less physical activity. However, we cannot test this hypothesis because of the cross-sectional design of the study. Furthermore, there was no data available regarding physical activity status before medication use.

The presence of an increase in symptoms in the morning was not associated with physical activity in this study. In patients with physician diagnosed COPD the regression coefficient was negative, indicating that patients with morning symptoms spent less MET-h/week in leisure time. This is in line with the notion that the morning is the most troublesome part of the day for COPD patients resulting in activity limitations.[37] In the total and newly diagnosed population, the regression coefficient was positive. We did not expect this result, since a systematic review has reported that morning symptoms were associated with less physical activity in COPD, also in non-severe COPD stages.[38] However, the difference in the direction of the regression coefficient can be due to the severity of airflow limitation or to symptom severity, since it was shown in previous studies that patients with more severe morning symptoms are those that also report in general more severe symptoms.[39] Furthermore, only 16% of patients reported an increase in symptoms in the morning in the present study. We speculate that the reporting of morning symptoms would be have been higher if there was an additional question in which patients had the possibility to score the severity of the symptoms, as in other studies.[40, 41] This would have likely resulted in a less positive (or a negative) regression coefficient in the total studied population.

Newly diagnosed patients reported a higher physical activity than those with physician diagnosed COPD, which could be explained by the presence of a higher degree of airflow limitation in patients with physician diagnosed COPD. It is known that physical activity is lower in more severe COPD stages.[6] Patients with physician diagnosed COPD were more likely to be treated with pulmonary medication. There was no difference in the presence of pulmonary symptoms between patients with physician diagnosed COPD and those with newly diagnosed COPD. This demonstrates that also those with previously undiagnosed COPD did experience symptoms, although their symptoms may have been less severe. Furthermore, it can be speculated that inactivity or activity limitations, rather than symptoms, are reasons for patients to seek medical attention. This is in line with a previous study reporting that COPD patients experience the physical effects associated with the occur-

rence of symptoms as a greater challenge than the symptoms themselves.[37] However, this suggestion was made based on reporting of morning symptoms and may not be fully applicable for symptoms in general.

Strengths and limitations

Since analyses were weighted for BMI, our cohort reflects a general COPD population in which the mean BMI is comparable to that in other COPD studies.[7, 15] A strength of this study was that patients with physician diagnosed and newly diagnosed COPD were included, while other studies only included patients with physician diagnosed COPD and thereby missed undiagnosed patients. The prevalence of COPD is underestimated[22] and half of the patients already have COPD GOLD 2 when the diagnosis is confirmed by spirometry.[42]

A limitation of this study is that patients might have been included with an obstructive pulmonary function but another diagnosis than COPD (for example asthma, acute and chronic bronchitis, bronchiectasis, cystic fibrosis, and bronchiolitis).[43] However, the incidences of these diagnoses are lower than for COPD, except for asthma. Patients with asthma or asthma-COPD overlap syndrome (ACOS) might have been included since data regarding reversibility in pulmonary function was not available. However, patients with a ICPC code R96, never smokers and those with a high Fe_{NO} (more likely to be asthma) were excluded to avoid misclassification. Including asthmatics might have resulted in an overestimation of physical activity since patients with asthma are as physically active as non-asthmatics.[44] Not having post-bronchodilator data can be seen as a weakness. However, this is inherent to population based studies and the results were also used in a previous report from our group.[45] For future studies in physical activity we suggest to include the non-smoking population as reference group. Another limitation of this study is the use of the SQUASH questionnaire to examine physical activity. However, this questionnaire has been used in a previous study that included COPD patients.[46] A disadvantage of the use of activity questionnaires is that many patients overestimate their physical activity.[47] However, when all patients overestimate their physical activity, associations with other patient characteristics will still be present. A third limitation is the limited sample size, which resulted in large confidence intervals for some characteristics. Although a larger sample size would have resulted in narrowing of confidence intervals and might have revealed more associations (for example a negative association between BMI and physical activity), the fact that we did detect the reported associations with a relative limited sample size also stresses their potential clinical relevance.

CONCLUSIONS

Patients with newly diagnosed COPD are more active than those with physician diagnosed COPD. The present study showed that in newly diagnosed patients pulmonary function was positively associated with physical activity. Furthermore, the use of LAMA and ICS/LABA/LAMA was negatively associated with physical activity in newly diagnosed patients. The most likely explanation is that patients with pulmonary medication experience more severe symptoms that result in less physical activity. In physician diagnosed patients an association between anxiety and working status, and physical activity was found. We found no association between education level, working status, smoking status, alcohol intake, BMI, depression, morning symptoms and physical activity. Intervention studies are needed to determine whether early pharmacological interventions and/or physical activity slow down COPD progression in non-severe COPD.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Medical Ethical Committee of the Leiden University Medical Center approved the study design. All participants gave their written informed consent.

CONSENT FOR PUBLICATION

Not applicable

DATA AVAILABILITY STATEMENTS

The dataset used and analysed during the current study are available from the corresponding author on reasonable request. Before this request, users should get permission from the local ethics committee.

COMPETING INTERESTS

All authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

Conception and design of the study, analysis and interpretation of data: AB, RH, MK, TB, RM, PH, SC, FR, NC and CT. Drafting the manuscript or revision: AB, RH, MK, TB, RM, PH, SC, NH and CT. All authors read and approved the final manuscript.

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LIST OF ABBREVIATIONS

BAI: Beck Anxiety Inventory
BMI: body mass index
CI: confidence interval
COPD: Chronic obstructive pulmonary disease
Fe_{NO}: fractional exhaled nitric oxide
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GOLD: global initiative for chronic obstructive lung disease
ICPC: International classification of primary care
ICS: inhaled corticosteroids
IDS: Inventory of Depressive Symptomatology
IQR: interquartile range
LABA: long-acting beta2 agonist
LAMA: long-acting muscarinic antagonist
MET-h/week: hours per week of metabolic equivalents
NEO: Netherlands Epidemiology of Obesity
SABA: short-acting beta2 agonist
SAMA: short-acting muscarinic antagonist
SD: standard deviation
SQUASH: Short Questionnaire to Assess Health-Enhancing Physical Activity

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Distribution of symptomatic and non-symptomatic patients with physician diagnosed and newly diagnosed early stage COPD

COPD stage	Percentage without pulmonary symptoms	Percentage with pulmonary symptoms
Physician diagnosed GOLD 0	41.9	58.1
Physician diagnosed GOLD 1	45.8	54.2
Newly diagnosed GOLD 1	49.5	50.5
Physician diagnosed GOLD 2	18.1	81.9
Newly diagnosed GOLD 2	29.1	70.9

COPD: Chronic obstructive pulmonary disease; GOLD: global initiative for chronic obstructive lung disease

A systematic diagnostic evaluation combined with an internet-based self-management support system for patients with asthma or COPD

Authors

Amanda R. van Buul[1]
Thomas S. Wildschut[1,2]
Tobias N. Bonten[1,2]
Marise J. Kasteleyn[1,2]
Annelies M. Slats[1]
Niels H. Chavannes[2]
Christian Taube[1,3]

Affiliations

[1]Dept of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands.
[2]Dept of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands.
[3]Dept of Pulmonary Medicine, West German Lung Center, Essen University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany.

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ABSTRACT

Introduction: An (inter)national systematic approach for patients with asthma COPD referred to secondary care is lacking. Therefore, a novel systematic approach was designed and tested in clinical practice.

Methods: This was a retrospective observational study of data from the electronic record system of the Leiden University Medical Center. Asthma and COPD patients were included if they were evaluated with a novel systematic approach or if they had a new record for asthma or COPD and received usual care. The novel systematic approach consisted of a predefined diagnostic evaluation combined with an optional internet-based self-management support system. Diagnostic tests, final diagnosis, lifestyle advices, symptoms and individual care plans in the electronic records, number of patients referred back to primary care, and time to referral back to primary care were compared between the systematic approach and usual care groups using *t*-tests and chi-squared tests.

Results: A total of 125 patients were included, of which 22 (21.4%) were evaluated with the systematic approach. Mean (±SD) age was 48.8 (±18.4) years and 59.2% were women. Mean (±SD) number of diagnostic tests was higher in the systematic approach group compared with the usual care group (7.6±1.0 vs 5.5±1.8, $P<0.001$). Similarly, in the systematic approach group, more lifestyle advices (81.8% vs 29.1%), symptom scores (95.5% vs 21.4%), and individual care plans (50.0% vs 7.8%) were electronically recorded ($P<0.001$), and more patients were referred back to primary care (81.8% vs 56.3%, $P=0.03$). There were no differences in the final diagnoses and time to referral back.

Conclusion: Our study suggested that not all tests that were included in the systematic approach are regularly needed in the diagnostic work-up. In addition, a designated systematic approach stimulates physicians to record lifestyle advices, symptoms, and individual care plans. Thus, this approach could increase the number of patients referred back to primary care.

Keywords: asthma, COPD, diagnostics, eHealth, outpatient clinic, systematic approach

INTRODUCTION

Asthma and COPD are common obstructive lung diseases. It is important to differentiate between asthma, COPD, and other (lung) diseases to phenotype these diseases even if the asthma/COPD is not severe as well as to design individual care plans. International guidelines have suggested on the parameters that should be assessed to evaluate asthma and COPD.[1-3] However, the guidelines do not provide suggestions on the additional tests that should be necessarily added to decrease the likelihood of other diagnoses, nor on the tests that should preferably be performed to identify treatable traits. A review showed that the use of care pathways results in a reduction of costs, improved quality of life, reduced number of complications, increased patient satisfaction, improved communication between doctors and nurses, and reduced time that healthcare providers spent carrying out paperwork.[4] However, for unknown reasons, a uniform international systematic approach for assessment of asthma and COPD patients referred to secondary care is lacking. Therefore, a diagnostic approach has been developed for asthma and COPD patients in the Netherlands. This diagnostic approach includes functional tests in addition to additional tests to acquire detailed insights into symptoms, functional limitation, and quality of life, ultimately to create a personalized treatment plan.[5] Patients are involved in this treatment plan in formulating their own treatment goals. However, it is thought that patient involvement could be increased by the use of eHealth. The previous diagnostic approach has been successfully implemented. However, the effects of the use of this diagnostic approach on the number of diagnostics, final diagnoses, referrals back to primary care, and long-term outcomes have not been evaluated yet. In addition, eHealth could be used as a method to integrate the individual care plans.[6] Therefore, in the LUMC, a novel systematic approach was developed that consisted of a predefined diagnostic evaluation combined with an optional internet-based self-management support system. Since March 2016, patients with (suspected) asthma or COPD who were referred by a GP to secondary pulmonary care were systematically evaluated with this systematic approach. The primary aim of this study was to determine whether there was a difference between the systematic approach and usual care in terms of type of diagnostic tests, number of diagnostic tests, final diagnosis, recorded lifestyle advices, symptoms and individual care plans in the electronic records, number of patients referred back to primary care, and time to referral back to primary care. The secondary aim of this study was to evaluate the number of patients who used the internet-based self-management support system. We hypothesize that a systematic approach could lead to a more specified diagnosis, more lifestyle advices, symptoms and individual care plans that are recorded in the electronic records, and more and faster referral back to primary care.

MATERIALS AND METHODS

Diagnostic pathway

Since March 2016, a novel systematic approach to evaluate patients with (suspected) asthma or COPD was released at the outpatient clinic of the department of pulmonology at the LUMC. A pulmonologist who was not involved in the study assessed the urge of the GP referrals. Patients with urgent complaints were scheduled at the outpatient clinic for acute respiratory complaints. The other patients were scheduled either within the novel systematic approach or by usual outpatient clinic care, depending on the first possibility at the outpatient clinic. With usual care, physicians decided which diagnostic tests to be performed based on outcomes of the clinical history and personal preferences. The systematic approach consisted of a predefined systematic diagnostic evaluation combined with an optional internet-based self-management support system. There were two or three visits, or more if there was a medical reason for additional diagnostic tests (Figure 1). During the first visit, a nurse practitioner obtained general information, vital parameters, and evaluated inhaler technique. The same day, lung function tests (spirometry before and after bronchodilation and DLCO) were performed. FeNO was measured and a chest X-ray, ECG, and laboratory tests (including hemoglobin, erythrocyte sedimentation rate, white blood cell count with differential, sodium, potassium, creatinine, radioallergosorbent test, thyroid stimulating hormone, N-terminal pro B-type natriuretic peptide, total immunoglobulin E, 25-hydroxyvitamin D, and alpha 1-antitrypsin) were performed. The nurse informed the patients about the internet-based self-management support system in the form of "PatientCoach". PatientCoach has been developed by the LUMC specifically for patients with chronic diseases and contains information about asthma and COPD, self-monitoring, an individual care plan, and e-visits.[7] The GP can also access PatientCoach. If a patient agreed to use PatientCoach, he or she was asked to complete the Nijmegen Clinical Screening Instrument[8] and asthma control questionnaire[9] or the clinical COPD questionnaire[10] at home. In addition, patients formulated their own personal treatment goals. During the second visit, the nurse practitioner discussed the outcomes of the questionnaires and the personal goals. The second visit was canceled if the patients refused to use PatientCoach.

During the last planned visit, a pulmonologist or a pulmonology resident discussed the outcomes of the diagnostic tests with the patient and an individual care plan was created. If a patient used PatientCoach, the individual care plan was integrated in PatientCoach. If additional diagnostic tests, eg, chest CT scan or sputum cultures, were needed, patients were scheduled for a fourth or later follow-up visit. If no more visits in the hospital were necessary, patients were referred back to primary care. The GP and the patient still had access to PatientCoach, enabling the continuation of eHealth in further care.

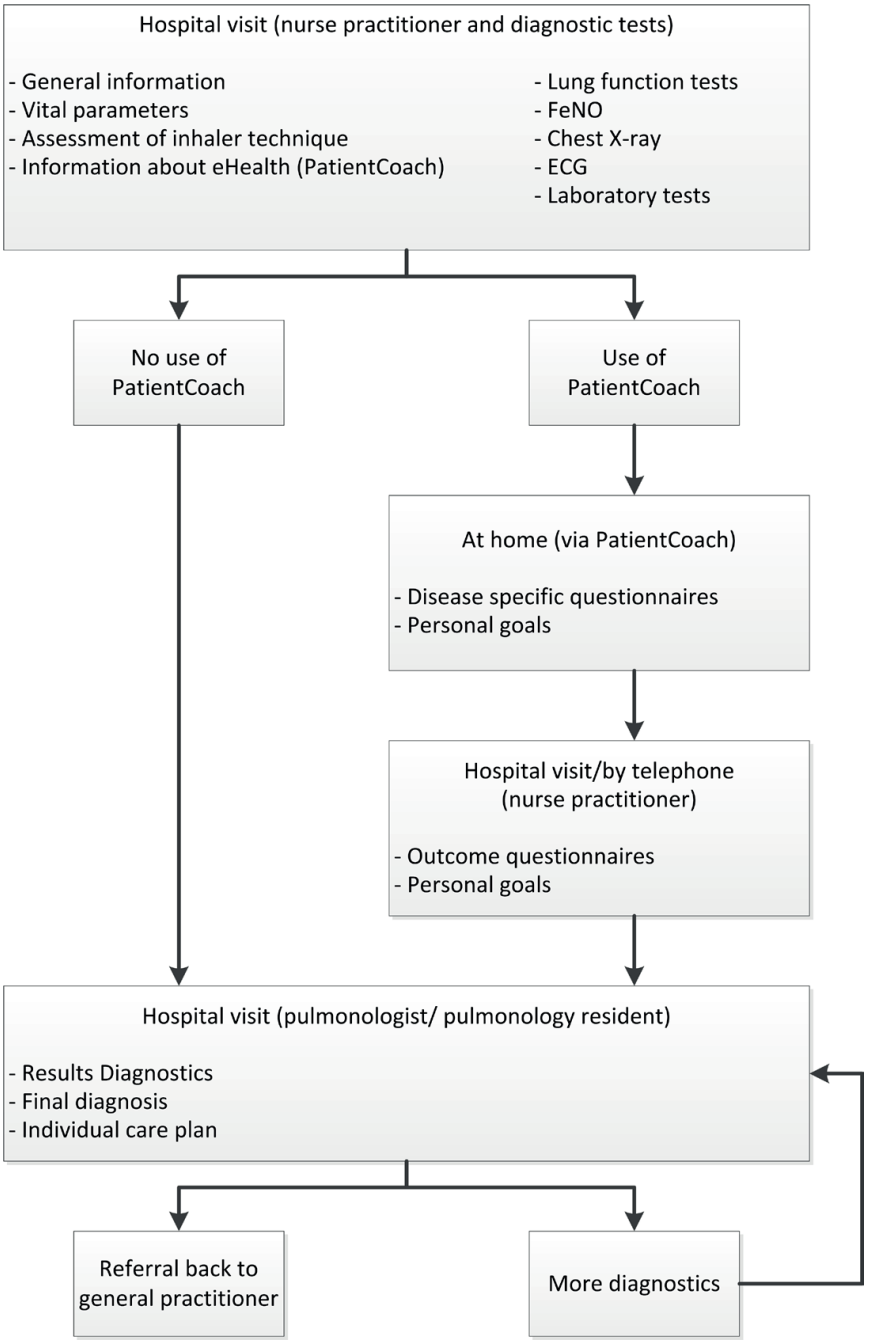

Figure 1 Novel systematic approach for asthma and COPD at the LUMC. ECG: electrocardiography; FeNO: Fractional exhaled nitric oxide; LUMC: Leiden University Medical Center.

Study design

This was a retrospective observational study of real-life data that were retrieved from the electronic record system of the LUMC. Data were collected between November 2017 and January 2018 from patients who attended the outpatient clinic of the LUMC for the first time between March 2016 and July 2017. The medical ethical committee of the LUMC waived the need for ethical approval due to the retrospective nature of the study. Consequently, the need for informed consent was not applicable.

Study population

Patients were included if they were evaluated with the systematic approach or if they had a new record for asthma or COPD and were evaluated by usual outpatient clinic care. Patients were included if they attended the outpatient clinic of the LUMC for the first time between March 2016 and July 2017. Patients were excluded if they attended the dyspnea clinic of the LUMC, if they had a previous record of asthma or COPD at the department of pulmonology at the LUMC, if they were solely admitted to the clinical ward; if they were not referred by a GP, if the first visit was at the emergency room or in the clinical ward, if the reason for referral was not asthma or COPD, or if the patient did not show up at the outpatient visits.

Data collection

Baseline characteristics were collected from the electronic records from the first visit at the department of pulmonology at the LUMC. Type of diagnostic tests, number of diagnostic tests, final diagnosis, lifestyle advices, symptoms and individual care plans in the electronic records, number of patients referred back to primary care, and time to referral back to primary care were collected from the electronic records as primary outcomes. The secondary outcome was the number of patients who used PatientCoach.

Diagnostic tests, needed for the work-up to the final diagnosis, were evaluated. The type of diagnostic tests that were assessed included laboratory tests, lung-specific laboratory tests (including arterial blood gas analysis, alpha-1 antitrypsin, and radioallergosorbent test), spirometry, histamine provocation test, FeNO, DLCO, chest X-ray, CT (including pulmonary CT angiography), bronchoscopy, sputum cultures, six-minute walking test, and ECG. The final diagnosis that was registered in the electronic records was evaluated. Predefined diagnoses were asthma, COPD, a combination of asthma and COPD, another pulmonary disease, no pulmonary disease, obesity-related symptoms, or no diagnosis. If the final diagnosis was asthma and/or COPD, the phenotype was evaluated. Predefined phenotypes included allergic, nonallergic, late-onset asthma, asthma with fixed airflow limitation, and asthma with obesity.[1] Alpha-1 antitrypsin deficiency, emphysema/hyperinflation, and frequent exacerbators[11] (including the GOLD group B and D[2]) were predefined phenotypes in COPD. The number of reported symptom scores, lifestyle advices, and individual care plans were collected from the electronic records. The number of patients who were referred back to primary care was collected. The number of days between referral and first visit, between first visit and final diagnosis, between first visit and the latest diagnostic test, and between first visit and referral back to primary care were calculated.

The number of patients who logged in at least once in PatientCoach was collected from the electronic records.

Statistical analysis

Patients with missing data on the key variables were excluded (N=2). Descriptive data were reported as percentages and mean values±SD for continuous variables. To compare means between the systematic approach and usual care groups for continuous baseline characteristics as age and BMI, unpaired *t*-tests were used. To compare percentages between the systematic approach and usual care groups for categorical baseline characteristics as percentage women and smoking status, chi-squared tests were used. To compare percentages of performed diagnostic tests between the systematic approach and usual care groups, chi-squared tests were used. To compare the mean time between referral and other time points and the mean number of performed diagnostic tests, between the systematic approach and usual care groups, unpaired *t*-tests were used. To compare percentages of final diagnosis as asthma and COPD, electronically recorded lifestyle advices, electronically recorded symptoms scores, electronically recorded individual care plans, and referrals back to primary care, between the systematic approach and usual care groups, chi-squared tests were used.

Since the use of PatientCoach was optional and a part of patients refused to use it, the number of patients who logged in at least once in PatientCoach was collected. The number of patients who logged in at least once in PatientCoach was expressed as percentage of the total number of patients who were included in the diagnostic approach. To compare means between patients in the systematic approach group who used PatientCoach and who did not for continuous baseline characteristics, unpaired *t*-tests were used. To compare percentages between patients in the systematic approach group who used PatientCoach and who did not, for categorical baseline characteristics, chi-squared tests were used. Furthermore, a sensitivity analysis was performed to evaluate the differences in primary outcomes between the patients in the usual care and those in the diagnostic approach who used PatientCoach. All analysis were conducted using SPSS version 23.0.

ETHICS STATEMENT

The medical ethical committee of the LUMC waived the need for ethical approval due to the retrospective nature of the study. Consequently, the need for informed consent was not applicable. Data that were entered in the database were de-identified.

RESULTS

General outcomes

In total, 125 out of 608 patients were included in the analysis (Figure 2), of which 22 (21.4%) were evaluated with the systematic approach. Baseline characteristics of all included patients are presented in Table 1. In total, 67.2% of patients were referred for asthma. Mean (±SD) age was 48.8 (±18.4) years and 59.2% of patients were women. There were no significant differences in baseline characteristics between patients who were evaluated with the systematic approach compared with usual care.

Diagnostic tests

The most frequently performed diagnostic test was spirometry (97.6%) (Table 2). The mean (±SD) number of diagnostic tests was significantly higher in the systematic approach group compared with the usual care group (7.6±1.0 vs 5.5±1.8). Laboratory tests, lung-specific laboratory tests, FeNO, DLCO, chest X-rays, and ECG were more frequently performed in the systematic approach group than in the usual care group.

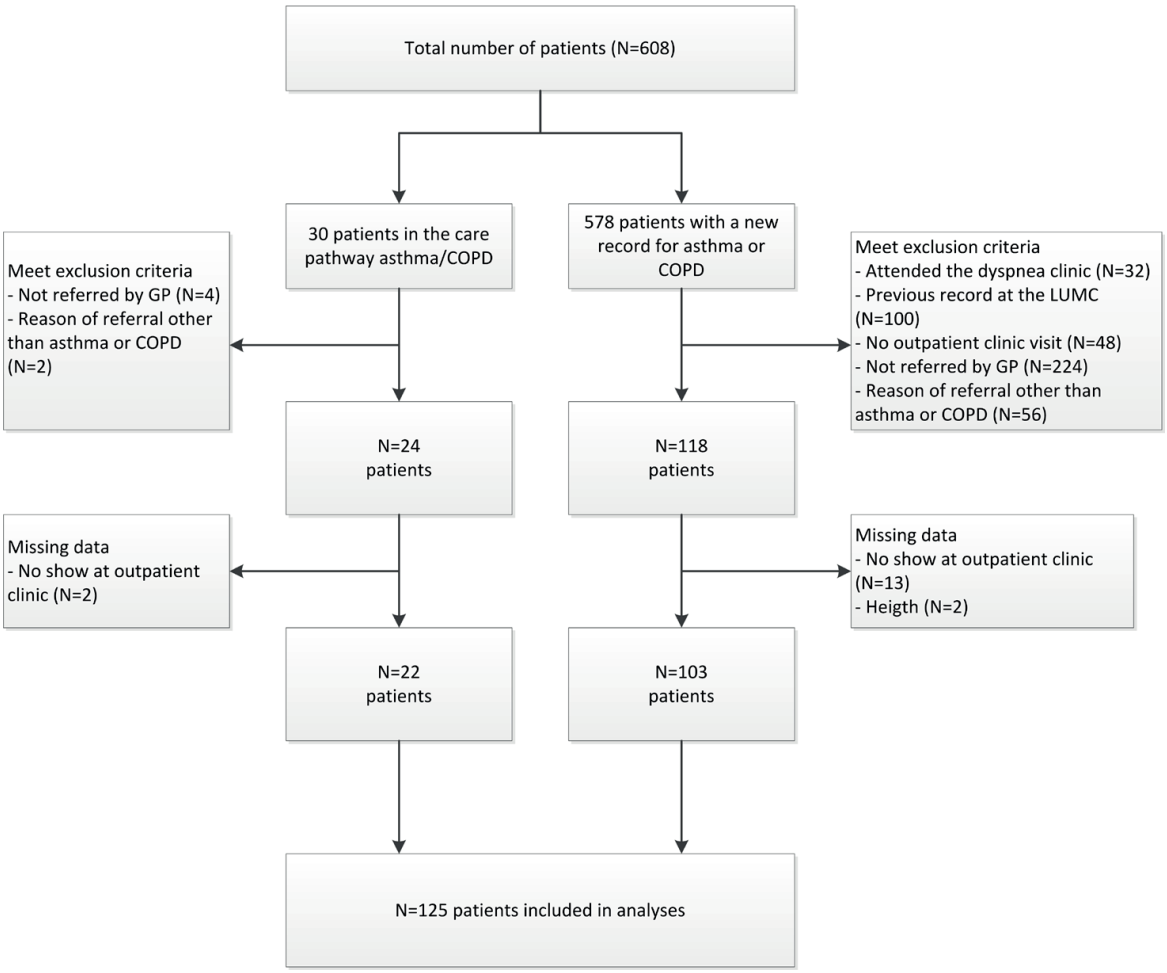

Figure 2 Flow diagram. GP: general practitioner; LUMC: Leiden University Medical Center

Table 1 Baseline characteristics

Characteristics	Total group (N = 125)	Usual care (N = 103)	Systematic approach (N = 22)	Difference (P-value)
Age in years (mean, (SD))	48.8 (18.4)	48.2 (18.2)	51.8 (19.5)	0.41
Sex, n (% women)	74 (59.2)	58 (56.3)	16 (72.7)	0.16
BMI in kg/m² (mean, (SD))	27.0 (6.8)	26.7 (6.7)	28.2 (7.6)	0.37
Cardiovascular comorbidities, n (% yes)	28 (22.4)	23 (22.3)	5 (22.7)	0.97
Reason of referral, n (% asthma)	84 (67.2)	69 (67.0)	15 (68.2)	0.91
Smoker status				
Never smoker, n (% yes)	55 (44.0)	43 (41.7)	12 (54.5)	0.27
Former smoking, n (% yes)	44 (35.2)	39 (37.9)	5 (22.7)	0.18
Current smoker, n (% yes)	26 (20.8)	21 (20.4)	5 (22.7)	0.81
Medication use at baseline				
SABA, n (% yes)	73 (58.4)	57 (55.3)	16 (72.7)	0.13
LABA, n (% yes)	79 (63.2)	63 (61.2)	16 (72.7)	0.31
SAMA, n (% yes)	16 (12.8)	14 (13.6)	2 (9.1)	0.57
LAMA, n (% yes)	29 (23.2)	23 (22.3)	6 (27.3)	0.62
ICS, n (% yes)	90 (72.0)	73 (70.9)	17 (77.3)	0.54
LTRA, n (% yes)	9 (7.2)	6 (5.8)	3 (13.6)	0.20
Antihistamines, n (% yes)	36 (28.8)	28 (27.2)	8 (36.4)	0.39

ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic-antagonist; LTRA: leukotriene receptor antagonist; SABA: short-acting beta2-agonist; SAMA: short-acting muscarinic-antagonist.

Table 2 Diagnostic tests at the outpatient clinic for the evaluation of asthma and COPD

Diagnostic tests	Total group (N = 125)	Usual care (N = 103)	Systematic approach (N = 22)	Difference (P-value)
Laboratory tests, n (% yes)	108 (86.4)	86 (83.5)	22 (100.0)	0.040
Lung-specific laboratory tests, n (% yes)	100 (80.0)	79 (76.7)	21 (95.5)	0.046
Spirometry, n (% yes)	122 (97.6)	100 (97.1)	22 (100.0)	0.42
Histamine provocation test, n (% yes)	40 (32.0)	34 (33.0)	6 (27.3)	0.60
Fe_{NO}, n (% yes)	85 (68.0)	64 (62.1)	21 (95.5)	0.002
DLCO, n (% yes)	88 (70.4)	66 (64.1)	22 (100.0)	0.001
Chest X-ray, n (% yes)	97 (77.6)	76 (73.8)	21 (95.5)	0.027
Chest CT scan, n (% yes)	23 (18.4)	18 (17.5)	5 (22.7)	0.56
Bronchoscopy, n (% yes)	1 (0.8)	1 (1.0)	0 (0.0)	0.64
Sputum cultures, n (% yes)	46 (19.2)	18 (17.5)	6 (27.3)	0.29
Six-minute walking test, n (% yes)	1 (0.8)	1 (1.0)	0 (0.0)	0.64
ECG, n (% yes)	38 (30.4)	18 (17.5)	20 (90.9)	<0.001
Number of diagnostic tests (mean (SD))	5.8 (1.9)	5.5 (1.8)	7.6 (1.0)	<0.001

CT: computed tomography; DLCO: diffusing capacity for carbon monoxide; ECG: electrocardiography; Fe_{NO}: fractional exhaled nitric oxide

Final diagnosis and registered symptom scores, lifestyle advices, and individual care plans

Most patients were finally diagnosed with asthma (53.6%), COPD (25.6%), or no pulmonary disease (9.8%). There were no differences in final diagnosis and phenotypes between the systematic approach and usual care groups (Table 3). In the systematic approach group, more lifestyle advices (81.8% vs 29.1%), symptom scores (95.5% vs 21.4%), and individual care plans (50.0% vs 7.8%) were electronically registered compared with the usual care group (all $P<0.001$).

Time to final diagnosis and referral back to primary care

There were differences in the number of days between referral and first visit (difference 4.4 days), between first visit and latest diagnostic test (difference 22.7 days), and between first

Table 3 Final diagnosis, phenotypes, and treatment plans in the diagnostic pathway compared with usual care

Final diagnosis and treatment	Total group (N = 125)	Usual care (N = 103)	Systematic approach (N = 22)	Difference (P-value)
Final diagnosis				
Asthma, n (%)	67 (53.6)	56 (54.4)	11 (50.0)	0.71
Phenotyped, n (% yes)	57 (85.1)	46 (82.1)	11 (100.0)	0.13
Allergic asthma, # n (% yes)	44 (65.7)	35 (62.5)	9 (81.8)	0.22
Non-allergic asthma, # n (% yes)	11 (16.4)	9 (16.1)	2 (18.2)	0.86
Late-onset, # n (% yes)	7 (10.4)	6 (10.7)	1 (9.1)	0.87
With fixed airflow limitation, # n (% yes)	4 (6.0)	4 (7.1)	0 (0.0)	0.36
Asthma with obesity, # n (% yes)	0 (0.0)	0 (0.0)	0 (0.0)	NA
COPD, n (%)	32 (25.6)	27 (26.2)	5 (22.7)	0.73
Phenotyped, n (% yes)	18 (56.3)	16 (59.3)	2 (40.0)	0.43
AAT deficiency, # n (% yes)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Emphysema/hyperinflation, # n (% yes)	6 (18.8)	6 (22.2)	0 (0.0)	0.24
Frequent exacerbations, # n (% yes)	12 (37.5)	10 (37.0)	2 (40.0)	0.90
Combination of asthma and COPD, n (%)	1 (0.8)	1 (1.0)	0 (0.0)	0.64
Phenotyped, n (% yes)	1 (100.0)	1 (100.0)	0 (0.0)	NA
Other pulmonary disease, n (% yes)	6 (4.8)	4 (3.9)	2 (9.1)	0.30
No pulmonary disease, n (% yes)	12 (9.6)	10 (9.7)	2 (9.1)	0.93
Obesity related symptoms, n (% yes)	3 (2.4)	2 (1.9)	1 (4.5)	0.47
No diagnosis, n (% yes)	2 (1.6)	2 (1.9)	0 (0.0)	0.51
Lifestyle advices, n (% yes)	48 (38.4)	30 (29.1)	18 (81.8)	<0.001
Symptom scores, n (% yes)	43 (34.4)	22 (21.4)	21 (95.5)	<0.001
Individual care plans, n (% yes)	19 (15.2)	8 (7.8)	11 (50.0)	<0.001

AAT: alpha 1 antitrypsin. #Patients could be categorised in more than one phenotype.

Table 4 Time between referral, first visit, final diagnosis, latest diagnostic test and referral back to primary care

Time	Total group (N=125)	Usual care (N = 103)	Systematic approach (N = 22)	Difference (P-value)
From referral to first visit in days (mean (SD))	37.7 (23.6)	38.4 (24.6)	34.0 (17.8)	0.43
From first visit to final diagnosis in days (mean (SD))	68.3 (88.0)	72.3 (91.7)	49.6 (66.9)	0.28
From first visit to latest diagnostic test in days (mean (SD))	116.7 (127.3)	122.7 (128.7)	88.6 (119.2)	0.26
Referred back to primary care, n (%)	76 (60.8)	58 (56.3)	18 (81.8)	0.03
Time from first visit and referral to primary care in days (mean (SD))	114.1 (97.7)	113.3 (96.0)	116.5 (105.8)	0.91

visit and final diagnosis (difference 34.1 days) between the systematic approach and usual care groups. However, these differences did not reach significance (Table 4). More patients in the systematic approach group were referred back to primary care compared with the usual care group (81.8% vs 56.3%, *P*=0.03).

Use of PatientCoach

In the systematic approach group, 14 out of 22 patients (63.6%) logged in at least once on PatientCoach. Patients who used PatientCoach were significantly younger and had less cardiovascular comorbidities than those who did not use PatientCoach. Reasons to refuse the use of PatientCoach were not having a computer (N=2), lack of computer skills (N=4), definitely no desire to use PatientCoach without a further reason (N=1), and for one patient the reason was not applicable.

Sensitivity analysis

After removing eight patients who attended the systematic approach, but refused the use of PatientCoach, the statistically significant differences between the systematic approach and usual care were still present (Supplementary tables S1 and S2).

DISCUSSION

This study was conducted to evaluate a systematic approach combined with an optional internet-based self-management support system for asthma and COPD patients referred to secondary care. In the systematic approach group compared with the usual care group, mean number of diagnostic tests was higher; more lifestyle advices, symptom scores, and individual care plans were electronically recorded; and more patients were referred back to primary care. There were no differences in final diagnosis and time to referral back.

More than half of patients were interested in an internet-based self-management support system when it was offered in addition to a systematic approach.

To our knowledge, this is the first study that evaluated a systematic approach in combination with an optional internet-based self-management support system as a method to evaluate diagnosis and symptoms and to integrate individual care plans in secondary care pulmonology. More diagnostic tests were performed in the systematic approach compared to usual care in the present study. This could be expected since the diagnostic approach consisted of more diagnostic tests than are stated in the guidelines. Since there were no differences in the final diagnoses made by pulmonologists and the process was not faster, this suggests that not all tests included in the systematic approach are regularly needed in the diagnostic work-up. In another systematic approach that has been developed for asthma and COPD patients in the Netherlands, other standard diagnostic tests were used: capillary blood gas analyses, metronome-paced hyperventilation test, and physical activity assessment by accelerometry were performed in all patients; X-rays, FeNO, and allergic assessment were performed only in selected patients.[5] Taking the results of the present study and the previous Delphi study into account, it can be suggested that lung-specific laboratory tests, DLCO, X-rays, FeNO, and an ECG should preferably be performed on indication and should not be included in a systematic approach in nonselected patients, since these additional tests did not lead to other diagnoses. This decision will decrease the number of diagnostic tests and thereby costs. On the other hand, it is possible that the additional diagnostic tests contributed more certainty to a diagnoses of asthma or COPD, resulting in more referrals back to primary care, as observed in our study. This follows the Dutch guidelines to refer patients back to primary care when the diagnostic work-up is completed and patients are clinically stable.[12] Another explanation of more referrals back to primary care might be the higher number of written care plans, since pulmonologists might believe that the care plans will support the GP and patients in the continuation of care. The present study shows that if physicians are directed to register individual care plans, this was done more frequently than with usual care. This is in line with a systematic review that the use of clinical pathways result in improved documentation.[13] We think that more than 48.5% of patients in the usual care group did receive lifestyle advices and individual care plans, but these advises were given verbally and were not necessarily registered in the medical records. However, international guidelines recommend written care plans and not solely spoken arrangements.[1, 2] A designated pathway within an outpatient clinic could thus add to improve registration of individual care plans.

The internet-based self-management support system was accepted by 63.6% of patients, which is in line with a previous study that showed that 63% of patients would definitely or probably use an eHealth application if it was offered.[14] In the present study, reasons to

refuse eHealth were mostly computer (skill) related. A previous study showed that patients who do not use eHealth do not recognize the advantages of eHealth and should be convinced first.[15] Patients who do have experience with the use of eHealth are positive.[15] The use of PatientCoach may be lower than 63.6%, because only the first login was evaluated, and it is known from previous research that some patients stop using the application.[16] Probably, more patients would use PatientCoach when previously determined barriers such as sufficient functionalities to tailor PatientCoach and personal guidance are further optimized.[17] An advantage of the use of eHealth is that patients considered eHealth as a possibility to take more responsibility in their own care.[15]

A strength of the present study was that the outcomes seem to be generalizable to all asthma and COPD patients referred to secondary care since we included nonselected patients and not only severe asthma and COPD patients. For difficult to manage asthma, systematic approaches exist[18, 19] with positive effects on asthma control, quality of life, and exacerbation frequency.[19] However, the results are only applicable for <15% of all asthma patients.[20] Care pathways for in-hospital management of exacerbated COPD exist, with positive effects on 30-day readmission rate. The present study shows that a systematic approach seems to be beneficial for all patients with asthma as well as COPD referred to secondary care pulmonology. However, we based our conclusions on a limited number of patients who were evaluated with the systematic approach. However, there were no differences in baseline characteristics compared with the usual care group that consisted of 103 patients. A limitation of the present study is the possibility of bias during the selection process whether patients were evaluated with the systematic approach or with usual care. This could have led to patients with less severe disease in the systematic approach since patients with acute complaints were evaluated at the outpatient clinic for acute respiratory complaints. However, there were no differences in the number of days between referral and first visit, suggesting that a limited number of patients within the usual care group were referred for acute respiratory complaints. Another limitation is that the data were retrieved from only one university hospital. This could have resulted in more complex disease combined with comorbidities. Consequently, the results could be less generalizable to local hospitals. However, in this study only patients who were referred by the GP were included and those who were referred for second or third opinion were excluded. A third limitation is that patients who were evaluated with the systematic approach were evaluated by a limited number of pulmonologists, whereas the patients who received usual care were seen by multiple pulmonologists of the department. We do not think this affected the results, since all patients in the systematic approach group were systematically evaluated and the pulmonologist could not influence the standard diagnostic tests, whereas in the usual care group, the diversity of physicians reduces the possibility of a physician-dependent preference for diagnostic work-up.

Giving the results of the present study, we recommend the use of systematic approaches that direct physicians to register lifestyle advices, symptoms, and individual care plans in daily practice, with a limited number of standard diagnostic tests. We recommend prospective evaluation of the impact of this systematic approach on disease control, quality of life, lifestyle changes, and costs.

CONCLUSION

A predefined systematic approach in combination with an optional internet-based self-management support system is useful in clinical practice. Since there were no differences in the final diagnoses, this suggests that not all tests that were included in the systematic approach are regularly needed in the diagnostic work-up. The outcomes suggest that a designated systematic approach stimulates physicians to record lifestyle advices, symptoms, and individual care plans. Subsequently, this approach could increase the number of patients referred back to primary care, according to national healthcare guidelines in the Netherlands.

DATA SHARTING STATEMENT

The data set used and analyzed during the current study are available from the corresponding author on reasonable request. Before this request, users should get permission from the medical ethical committee of the LUMC.

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AUTHOR CONTRIBUTIONS

Design of the study: ARvB, TNB, MJK, AMS, NHC, and CT. Data analysis: ARvB and TSW. Data interpretation: ARvB, TSW, TNB, MJK, AMS, NHC, and CT. Drafting the manuscript: ARvB, TSW, and TNB. Revision of the manuscript: ARvB, MJK, AMS, NHC, and CT. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

DISCLOSURE

The authors report no conflicts of interest in this work.

LIST OF ABBREVIATIONS

CT: computed tomography
DLCO: diffusing capacity for carbon monoxide
ECG: electrocardiography
FeNO: fractional exhaled nitric oxide
GOLD: Global Initiative for Chronic Obstructive Lung Disease
GP: general practitioner
ICS: inhaled corticosteroids
LABA: long-acting beta2-agonist
LAMA: long-acting muscarinic-antagonist
LTRA: leukotriene receptor antagonist
LUMC Leiden University Medical Center
SABA: short-acting beta2-agonist
SAMA: short-acting muscarinic-antagonist

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Final diagnosis, phenotypes and treatment plans in the diagnostic pathway compared with usual care

Final diagnosis and treatment	Total group (N = 117)	Usual care (N = 103)	Systematic approach (N = 14)	Difference (P-value)
Final diagnosis				
Asthma, n (%)	65 (55.6)	56 (54.4)	9 (64.3)	0.48
Phenotyped, n (% yes)	55 (84.6)	46 (82.1)	9 (100)	0.17
Allergic asthma,[#] n (% yes)	43 (66.2)	35 (62.5)	8 (88.9)	0.12
Non-allergic asthma, [#] n (% yes)	10 (15.4)	9 (16.1)	1 (11.1)	0.70
Late-onset, [#] n (% yes)	6 (9.2)	6 (10.7)	0 (0.0)	0.30
With fixed airflow limitation, [#] n (% yes)	4 (6.2)	4 (7.1)	0 (0.0)	0.41
Asthma with obesity, [#] n (% yes)	0 (0.0)	0 (0.0)	0 (0.0)	NA
COPD, n (%)	29 (24.8)	27 (26.2)	2 (14.3)	0.33
Phenotyped, n (% yes)	17 (58.6)	16 (59.3)	1 (50.0)	0.80
AAT deficiency, [#] n (% yes)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Emphysema/hyperinflation, [#] n (% yes)	6 (20.7)	6 (22.2)	0 (0.0)	0.45
Frequent exacerbations, [#] n (% yes)	11 (37.9)	10 (37.0)	1 (50.0)	0.72
Combination of asthma and COPD, n (%)	1 (0.9)	1 (1.0)	0 (0.0)	0.71
Phenotyped, n (% yes)	1 (100)	1 (100)	0 (0.0)	NA
Other pulmonary disease, n (% yes)	5 (4.3)	4 (3.9)	1 (7.1)	0.57
No pulmonary disease, n (% yes)	11 (9.4)	10 (9.7)	1 (7.1)	0.76
Obesity related symptoms, n (% yes)	2 (1.7)	2 (1.9)	0 (0.0)	0.60
No diagnosis, n (% yes)	2 (1.7)	2 (1.9)	0 (0.0)	0.60
Lifestyle advices, n (% yes)	43 (36.8)	30 (29.1)	13 (92.9)	<0.001
Symptom scores, n (% yes)	36 (30.8)	22 (21.4)	14 (100)	<0.001
Individual care plans, n (% yes)	16 (13.7)	8 (7.8)	8 (57.1)	<0.001

AAT: alpha 1 antitrypsin. [#]Patients could be categorised in more than one phenotype.

Supplementary table 2. Time between referral, first visit, final diagnosis, latest diagnostic test and referral back to primary care

Time	Total group (N=117)	Usual care (N = 103)	Systematic approach (N = 14)	Difference (P-value)
From referral to first visit in days (mean (SD))	37.7 (23.7)	38.4 (24.6)	32.1 (14.1)	0.35
From first visit to final diagnosis in days (mean (SD))	69.6 (89.3)	72.3 (91.7)	49.7 (69.4)	0.38
From first visit to latest diagnostic test in days (mean (SD))	119.3 (128.3)	122.7 (128.7)	94.0 (127.0)	0.43
Referred back to primary care, n (%)	70 (59.8)	58 (56.3)	12 (85.7)	0.04
Time from first visit and referral to primary care in days (mean (SD))	117.5 (97.9)	113.3 (96.0)	137.7 (108.6)	0.44

Discussion

INTRODUCTION

The aim of this thesis was to gain more knowledge about morning symptoms and physical activity in chronic obstructive pulmonary disease (COPD) in search of novel treatment options. According to the latest information of the World Health Organisation (WHO), COPD is the third leading cause of death worldwide.[1] There are no curative options for COPD yet. Major treatment goals in COPD are reduction of symptoms and prevention of acute exacerbations. However, COPD is still in the top five leading causes of disability-adjusted life-years.[2] Therefore, more research is needed into factors that are related with poor outcomes in COPD to encourage the development of novel treatment options. In this thesis there is a focus on morning symptoms and physical activity.

COPD is responsible for pulmonary symptoms such as dyspnoea, chronic cough and sputum production, which can occur during any part of the day. Patients reported the morning as most problematic part of the day.[3] After having been overlooked for several years, the first study of morning symptoms in COPD was published in 2009. Nowadays, it is known that the majority of COPD patients suffers from symptoms in the morning.[3-10] However, the relation between morning symptoms and other patient characteristics is not extensively studied hitherto.

Patients with COPD are less physically active when compared to their healthy peers.[11, 12] Low self-reported activity levels are associated with poor outcomes, such as higher mortality rates and hospitalizations.[13] It is difficult to increase physical activity, because regular physical activity is a lifestyle choice. In COPD, health related factors play an important role as well; pulmonary symptoms and fatigue are frequently mentioned as barriers to perform activities. There is a negative association between morning symptoms and physical activity. However, in earlier studies physical activity was self-reported, and the relation between objectively measured physical activity and morning symptoms has not been studied yet.

The studies described in this thesis target morning symptoms and physical activity. Furthermore, the association between objectively measured physical activity and morning symptoms is studied. The studies described in this thesis include a systematic review, results of a cross-sectional observational study, cross-sectional analyses of a previous cohort study and a real life study. In the current chapter, general conclusions from those studies are presented. Then, the discussion continues with methodological considerations. Thereafter, we discuss the questions whether morning symptoms cause physical inactivity and whether morning symptoms are a distinct phenotype in COPD. Then, we give our perspectives on the use of systematic approaches in secondary care pulmonology. Finally, we provide directions for future research and clinical practice.

GENERAL CONCLUSIONS

In the studies in this thesis, we highlighted that morning symptoms and physical activity are important for COPD patients, especially for those with more symptomatic COPD. From existing evidence, we concluded that there was a negative association between morning symptoms and self-reported physical activity. We confirmed this association in the MOrning symptoms in-Depth observationAl Study (MODAS), whereby we objectively measured physical activity. Furthermore, we were the first group that looked at activity patterns during the course of the day while taking morning symptoms into account. We showed differences in the number of steps in the morning and afternoon between patients with high morning symptom scores when compared to patients with low morning symptom scores. Thus, morning symptoms and physical activity are associated and they are important targets for therapy in moderate to very severe COPD. Also, we showed that there is an association between lower health status, increased anxiety and depression, lower physical activity, lower pulmonary function and morning symptoms. Furthermore, we observed in non-severe COPD that pulmonary function was associated with physical activity. Those findings make morning symptoms and physical activity even more interesting as a target for intervention. With our research, we gained new insights for future (interventional) studies in morning symptoms and physical activity in COPD. Furthermore, for clinical practice we encourage the use of a systematic approach for patients with (suspected) asthma and COPD referred to secondary care pulmonology, since we showed that a systematic approach stimulates physicians to record lifestyle advice including physical activity, symptoms and individual care plans.

METHODOLOGICAL CONSIDERATIONS

In research it is important to design high quality studies and minimize the risk of bias. [14] In studies that investigate symptoms or lifestyle as physical activity in general, we should be aware that the results of the studies may suffer from selection bias. The most symptomatic or disabled patients probably do not participate in such studies. Thus, the studies presented in this thesis may be less generalizable for the most symptomatic and disabled patient group.

Study designs

The studies described in this thesis include a systematic review, results of a cross-sectional observational study, cross-sectional analyses of a previous cohort study and a real life study. All study designs have their advantages and disadvantages.[15] Systematic reviews and meta-analyses are at the top of the evidence based medicine hierarchy.[14] However, in the

systematic review included in this thesis, outcomes from previous studies were not always comparable, since different tools were used to assess morning symptoms and physical activity. Therefore, a pooled meta-analysis was not possible. Cross-sectional observational studies are designed to test a hypothesis in a prespecified patient population, under optimal circumstances and controlled for confounders. A main advantage of cross-sectional studies is that they can be used to identify new research fields. In the MODAS, this was the association between morning symptoms and objectively measured physical activity. In the Netherlands Epidemiology of Obesity (NEO) study, these were patient characteristics of non-severe COPD patients that were related with physical activity. On the other hand, disadvantages of cross-sectional studies are that outcomes are less generalizable to real life situation due to the optimally created circumstances and longitudinal outcomes are lacking. For example, in the NEO study the use of nearly all pulmonary medication was associated with less physical activity. However, we did not know the physical activity levels before the use of pulmonary medication, resulting in the situation that we were probably looking at already improved activity levels. Real life studies do not have this disadvantage, but they have low internal validity and registration can be suboptimal. In this thesis, different study designs contributed to different outcomes. However, different study populations, different morning symptom questionnaires and different tools to assess physical activity also contributed to differences in results, and will be discussed in the next paragraphs.

Study population

Morning symptoms and physical inactivity are already present in non-severe COPD stages. Therefore, it is important to study all disease stages. In the systematic review, the severity of COPD was not an in- or exclusion criterion. In the NEO study, patients were included in the analyses if they had physician diagnosed COPD with an International Classification of Primary Care (ICPC) code for COPD (R95) or if patients met our criteria for newly diagnosed COPD. Patients with a forced expiratory volume in 1 second (FEV_1) <50% were excluded, since the focus of the study was on non-severe COPD. In this study, 76% of patients met the criteria for newly diagnosed COPD. This could have influenced the outcomes, since probably some of the patients do not suffer from COPD and suffer from another obstructive pulmonary disease such as asthma. Participants of the NEO study were recruited by general practitioners or through advertisements. In contrast, patients who participated in the MODAS, were those with moderate to very severe COPD and they were mainly recruited at the department of pulmonology in hospitals. COPD patients treated in secondary care pulmonology have in general more exacerbations, high symptom scores, coping problems, severe to very severe airway obstruction or hypoxia.[16] Patients who participated in the MODAS have a high burden of disease and were in advance more likely to have morning symptoms or activity limitations when compared to patients with a low burden of COPD who participated in the NEO study.

Morning symptom questionnaire

The use of different morning symptom questionnaires largely contributed to different occurrence rates of morning symptoms. For many years, researchers created their own morning symptom questionnaires that did not undergo a validation process.[6, 17-22] For explorative research in this field, we agree with the use of non-validated questionnaires. In the NEO study, that was a large population-based cohort study that was designed to help better understand development of diseases especially in obesity, participants filled in one non-COPD specific question about the increase of symptoms in the morning. Participants were not able to rank the severity of their morning symptoms. We think that the outcome of this question would have been different if there was an additional question about the severity of symptoms. It is reasonable to suppose that more patients would have filled in that they experience symptoms in the morning if this additional questionnaire was present, because it is known that patients with COPD tend to underestimate their symptoms if they are not severe enough, in their experience.[23] Furthermore, the time period of the morning was not clearly defined, whereby it could be unclear for participants whether they should rate their symptoms at the moment of awaking or during the entire morning. In the MODAS the primary outcome of the study was morning symptom severity. The PRO-morning COPD Symptom questionnaire was used to evaluate these symptoms. The PRO-morning COPD Symptom questionnaire is a six itemed questionnaire that was especially developed to evaluate morning symptoms in COPD. The pre-bronchodilator mean morning symptom score in the MODAS was only slightly higher than in a previous study that used this morning symptom questionnaire as well.[19] This questionnaire is not validated, but seems to be a reliable method to assess morning symptoms since the mean score in the MODAS was nearly comparable with mean morning symptom score in the above mentioned study. Furthermore, the six included questions in the questionnaire are in accordance with a recent validated morning symptom questionnaire.[24] This validated questionnaire consists of a 6-item symptom severity score, an overall symptom severity score, an activity limitation score, the use of rescue medication and includes a clear definition of the morning period. Thus, in the NEO study the occurrence of morning symptoms may be underestimated, while in the MODAS the occurrence of morning symptoms seems more reliable. For future research, we encourage the use of a validated morning symptom questionnaire. Using the same questionnaire results in more comparable outcomes and the minimal clinical important difference can be estimated.

Physical activity assessment

Physical inactivity is common in COPD and associated with poor patient related outcomes. [13] Therefore, it is important to search for factors that influence physical activity. In the NEO study, the short questionnaire to assess health-enhancing physical activity (SQUASH) [25] was used. It should be noted that the SQUASH has not frequently been used in

COPD patients. A disadvantage of the use of activity questionnaires in general is that patients overestimate standing time and underestimate sitting time.[26] However, in a large population-based cohort study it used to be too expensive and too time consuming to use objective methods to assess physical activity. Though, nowadays, with new technologies as smartphones with integrated pedometers, it is possible to objectively measure physical activity in large groups of patients. However, the use of smartphones is relatively new in this field and needs to be validated in COPD patients.[27, 28] In the MODAS, the international physical activity questionnaire (IPAQ) was used to evaluate which activities were performed. Furthermore, the MoveMonitor, a validated accelerometer,[29, 30] was used to assess physical activity. Patients were instructed to wear the accelerometer day and night for seven consecutive days. This resulted in 24-hour real life physical activity recording. Results of objectively measured physical activity as shown in **chapter 3** were not in accordance with the results of the IPAQ in **chapter 4**. This confirms that patients overestimate self-reported physical activity levels. Thus, we should carefully interpret physical activity that was evaluated with questionnaires. However, accelerometers have disadvantages as well. In the MODAS the major disadvantages of the used accelerometer were the lack of adherence to the wearing instructions, absence of difficulty scores and the non-water resistance of the accelerometer. In the MODAS 6% of the measured days were not included in the analyses due to non-adherence to wearing instructions vs. 1% of patients in the NEO study that did not complete the activity questionnaire. Furthermore, accelerometers do not capture the experience and difficulty of physical activity. Experience and difficulty are important for patients. It was reported that patients consider the physical effects associated with the occurrence of symptoms in the morning as a greater challenge than the symptoms themselves.[9] Therefore, in 2015 a PROactive tool was developed that combined variables retrieved from accelerometry with difficulty scores retrieved from a questionnaire.[31] Also, the accelerometer is not water resistant. In the context of physical inactivity due to morning symptoms, this is an important limitation, since most self-care routines such as taking a shower or bathing are undertaken in the morning. This could have resulted in an underestimation of physical activity in the morning. Since we used an accelerometer, we could compare the number of steps taken during different parts of the day between patients with high and low morning symptom scores **(chapter 4)**. This study was the first study that described activity patterns during the course of the day while taking morning symptoms into account.

MORNING SYMPTOMS CAUSE PHYSICAL INACTIVITY, OR IS IT THE OTHER WAY AROUND?

The morning is the most symptomatic part of the day for patients with COPD.[3] One of the factors that is negatively associated with morning symptoms is physical activity **(chapter 2)**, which we confirmed in the MODAS, using an accelerometer to objectively measure physical activity **(chapter 3)**. **Chapter 4** showed that patients with low morning symptom scores took more steps in the morning and in the afternoon than patients with high morning symptoms scores. Given the results of previous studies and the MODAS, the following question arises: are morning symptoms the reason why patients are inactive? Or is it the other way around, and is physical inactivity the reason why patients have symptoms in the morning? We will discuss the hypotheses "morning symptoms cause physical inactivity" and "physical inactivity causes morning symptoms" based on existing evidence.

Morning symptoms cause physical inactivity

If morning symptoms cause physical inactivity, morning symptoms will be an important target for intervention. Patients experience symptoms as an important barrier to being physically active.[32, 33] Dyspnoea has been shown to be the most important factor to explain physical inactivity.[34] Dyspnoea is one of the most common **(chapter 2)** and most severe **(chapter 3)** symptoms in the morning. The morning is the most active period of the day in which many self-care activities are undertaken that can cause or worsen symptoms.[22] Physical inactivity could be a coping mechanism to avoid or reduce symptoms. Many patients with COPD reported that they reduce physical activities and changed their morning routines due to symptoms.[8] Physical inactivity resulting in less symptoms, could be the explanation why we found no association between morning symptoms and physical activity in the NEO study **(chapter 5)**. In the MODAS, patients with high morning symptom scores spend a comparable number of minutes on moderate to vigorous intensity physical activity when compared to patients with low morning symptoms scores. However, when looking at bouts of at least ten minutes, these patients spend significantly less minutes doing moderate to vigorous intensity physical activity. This suggests that patients are able to be physically active, but their stamina is decreased. Thus, morning symptoms can cause serious physical activity limitations that need to be recognised.

Previous studies have shown positive effects of inhaled medication on morning symptoms and physical activity. [4, 6, 8, 22, 35-37] This indicates that there could be causality between morning symptoms and physical activity: when morning symptoms were improved, physical activity was improved as well. It should be noted that the effect of an once-daily formula in the evening on morning symptoms has not been studied yet. Since pulmonary symptoms vary over the day,[5] studying the effects of taking medication during differ-

ent parts of the day is necessary. Another promising method to decrease symptoms and increase physical activity is the combination of interventions, such as the combination of a self-management program with bronchodilators.[38]

Physical inactivity causes morning symptoms

It could also be true that physical inactivity is the cause of morning symptoms. Physical inactivity results in a downward spiral of muscular disuse, muscular dysfunction,[39] muscular depletion and deconditioning.[40] The lower limbs are affected, as well the diaphragmatic muscles. One third of patients with COPD have muscular dysfunction, including in the early stages of the disease. Deconditioning and muscle weakness cause progressive shortness of breath during exercise. Thus, the consequences of physical inactivity contribute to symptoms. We think that symptoms in general can be extrapolated to morning symptoms, because in this context, the underlying origin is the same. Whereas exercise causes a temporary increase in symptoms, prolonged periodic exercise finally results in more fatigue-resistant muscles.[41] The American College of Sports and Medicine recommends to perform 8 to 10 muscle strength exercises on two or more non-consecutive days each week[42]. COPD patients are encouraged to follow this recommendation, to become less symptomatic.

In conclusion, yet, both hypotheses could be true since prospective studies in this field are lacking and the existing evidence mostly stems from observational studies. Previous qualitative studies clearly showed that patients experience struggles in the morning due to morning symptoms. Therefore, we conclude that morning symptoms cause activity limitations. On the other hand, other previous studies showed muscle dysfunction in COPD on molecular base. Therefore, we have to search for (a combination of) interventions that target morning symptoms as well physical activity.

ARE MORNING SYMPTOMS TO A DISTINCT PHENOTYPE IN COPD?

In obstructive lung diseases, phenotyping has become more an important topic. In the last years, it has become apparent that different phenotypes in COPD patients need different therapeutic approaches. Patients with higher blood eosinophil counts seem to benefit from inhaled corticosteroids,[43] while the use of bronchodilators results in improvement of exercise performance in patients with dynamic hyperinflation.[44] Phenotyping can result in more tailored treatment on an individual patient level. It would be of interest if patients with high morning symptoms comprise a distinct phenotype and become a new treatable phenotype in COPD.

Definition of a phenotype

One previous study that investigated the hypothesis that morning symptoms are a distinct phenotype of highly symptomatic patients not captured by Clinical COPD Questionnaire, concluded that morning symptoms belong not a distinct phenotype in COPD.[45] This was based on the fact that only a small proportion of patients with low or slightly lower COPD health status, had high morning symptoms scores.[45] However, before we can speak about a phenotype, we should have a broader look at the definition of a phenotype. A phenotype in COPD has been defined as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes."[46] Hitherto, the predictive value of morning symptoms for meaningful outcomes as symptoms, exacerbations, disease progression and mortality are not well known. The MODAS was a cross-sectional study, so did also not contribute to the predictive value of morning symptoms. Increasing the knowledge of the aetiology of morning symptoms can be helpful to inform the discussion on phenotyping better.

Possible aetiology of morning symptoms

Yet, the aetiology of morning symptoms is not known. Morning symptoms are not an independent factor in COPD, but are dependent on multiple other factors that can be influenced. Here we discuss associated characteristics that are described in **chapter 3** as possible underlying mechanisms of morning symptoms. First, pulmonary function was associated with morning symptoms. Possibly, morning symptoms reflect the circadian variation of pulmonary function, since the worst pulmonary function is between 3 and 6a.m.[47] However, not all patients experience morning symptoms on each day and pulmonary function is only poorly correlated with symptoms in general.[48] Therefore, the severity of airflow limitation does contribute to symptoms in the morning, but it is not the only factor. Another characteristic that was associated with morning symptoms is lower health status. Health status reached the highest explained variance for morning symptoms in the MODAS. The association has been described frequently in previous studies.[9, 10, 45, 49, 50] In the MODAS, morning symptoms were associated with increased anxiety and depression and this association was also found in previous studies, although causality is not known.[7, 9, 10, 49] A previous study showed that dyspnoea is the symptom that concerns patients the most.[51] Anxiety for dyspnoea can lead to a down-ward spiral of anxiety-induced dyspnoea and further increased anxiety.[52] These factors together can contribute to symptoms in the morning. Another characteristic that was associated with morning symptoms in the MODAS was higher burden of symptoms. Maybe, the persistent high symptom scores are due to different types of dyspnoea with different underlying mechanisms. Whereas air hunger is caused by chemoreflex activity which is inhibited by pulmonary (hyper)inflation; the feeling of increased work of breathing is caused by muscle weakness; chest tightness is caused by bronchospasm; and tachypnoea is caused

by stimulation of pulmonary C fibres.[53] It is known from previous research that morning symptoms are associated with symptoms in other parts of the day, such as the evening and night.[7, 10, 45] This suggests that there is a factor in these patients that persists over the day that causes symptoms during several parts of the day. This might be due to local inflammation that causes mucus hypersecretion[54] and increased systematic inflammation that contributes to more exacerbations.[55] In **chapter 4**, patients with high morning symptoms scores were more likely to have had an exacerbation in the previous year when compared to patients with low morning symptom scores. In **chapter 3**, in the unadjusted regression analysis, there was also an association between morning symptoms and exacerbations. The association between morning symptoms and exacerbations has been described frequently. [7, 9, 45] It was suggested in a previous study that there might be an overlap between the chronic bronchitis phenotype and the patient group with morning symptoms.[9]

Other underlying mechanisms that may cause morning symptoms, but have to our knowledge not been studied, include sputum retention during the night, immune mediated causes and circadian variation in cortisol levels. When asleep, cough reflex sensitivity is diminished when compared to a waking state and there are less external stimuli that induce cough.[56] Impaired cough during the night can cause sputum retention during the night, which results in symptoms, such as cough and dyspnoea in the morning. We also hypothesize that the immune system influences symptoms in the morning. In asthma and allergy, which are T-helper 2 (Th2) diseases, patients experience an increase of symptoms in the morning.[57] If patients with morning symptoms are those with more Th2 inflammation, this can be the cause of morning symptoms. Finally, pulmonary function is not the only system with a circadian variation. There is a possibility that circadian variation in cortisol levels may affect morning symptoms as well. The cortisol awakening response occurs 30 to 45 minutes after awakening and during sleep the level drops to the lowest point.[58, 59] Altered responses in cortisol have been shown to be associated with psychological disorders as fatigue and depression. Depression is associated with morning symptoms. Furthermore, a recent study among police officers showed that sufficient physical activity could be protective against diminished awaking cortisol levels that were associated with poor sleep quality.[60]

We can conclude that morning symptoms are related to other factors that are associated with poor outcomes in COPD. However, it is not possible yet to state that morning symptoms are a distinct phenotype in COPD since we should first know the effects of morning symptoms on long term. In this chapter, we provided several relevant factors that can be studied to enlarge our knowledge about morning symptoms, which is needed to verify whether morning symptoms are a distinct phenotype in COPD.

SHOULD PULMONOLOGISTS EVALUATE ALL COPD PATIENTS WITH A SYSTEMATIC APPROACH?

An (inter)national systematic approach for COPD patients referred to secondary care does not exist. However, it be questioned whether pulmonologists need a systematic approach to diagnose obstructive lung diseases and improve treatment plans. Previous studies have shown that physicians do not always adhere to guidelines, because of low familiarity with the guidelines, low self-efficacy, and time constraints.[59] In **chapter 6**, we found that more lifestyle advice, more symptom scores and more individual care plans were recorded in the electronic records of patients who were evaluated with the systematic approach when compared to usual care. However, the systematic approach did not contribute to a more specific diagnosis. The outcomes of the study suggest that conditions and impact of COPD become more emphasized when a systematic approach is used when compared to usual care. This is in line with the fact that clinicians are most likely to discuss domains that are related to clinical features.[61] Therefore, we recommend the use of systematic approaches in clinical practice. We encourage to include morning symptoms and physical activity assessments in systematic approaches as well. Morning symptoms are common and important for COPD patients. However, these symptoms are not mentioned in international COPD guidelines and statements yet.[62] This might be due to that the awareness for morning symptoms is relatively new in COPD after being overlooked for several years. When morning symptoms are integrated in upcoming guidelines and statements, we expect that physicians will often forget to ask about morning symptoms, because they are not used to doing it, even though. Patients have reported that they need to discuss morning symptoms.[8] When integrated in a systematic approach, this could help to facilitate the discussion and awareness. In the real life study **(chapter 6)**, there was no physical activity assessment included in the systematic approach, although it was included in the outcome lifestyle advice. However, including objectively measuring physical activity, will help to get insight in actual physical activity levels, since it is difficult for patients to correctly estimate activity levels. Furthermore, it will lead to the recognition of physical inactivity and adverse effects of physical inactivity. We are aware that the implementation of objective physical activity assessments will result in large-scale use of accelerometers resulting in higher costs. Also, expertise in evaluating physical activity patterns is needed. However, an accurate measurement of physical activity gives opportunities regarding patient tailored activity recommendations. We think that new technologies as smartphones with integrated pedometers provide a relatively easy method to objectively measure physical activity. However, the use of such tools in clinical practice needs to be validated in future studies.[27, 28]

DIRECTIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

As discussed above in the discussion section, more research is needed to further increase the knowledge about morning symptoms and the relation with physical activity. First, the aetiology of morning symptoms should become more clear. Various factors, such as health status, anxiety and depression, physical activity, pulmonary function, exacerbations, sputum retention during the night, immune mediated causes and circadian variation in cortisol levels can be studied in the light of morning symptoms. When designing prospective studies, meaningful outcomes such as symptoms, exacerbations, disease progression and mortality should be used. With the results of such studies, we can determine whether morning symptoms constitute a distinct phenotype in COPD. Hopefully, the outcomes will encourage the integration of morning symptoms in future guidelines, statements and systematic approaches. For future research in the morning symptoms field, we recommend the use of a validated morning symptom questionnaire. Morning symptoms are not severe in all COPD patients. We think that patients who are referred to secondary care pulmonology are more prone to have more severe morning symptoms. Especially in this patient group, physicians should carefully assess morning symptoms in addition to general COPD-specific questionnaires. To implement this in usual care, we recommend the use of systematic approaches, since this improves the documentation of symptoms. Morning symptoms can be treated with medication. However, the effect of an once-daily formula in the evening on morning symptoms has not been studied yet. Since pulmonary symptoms vary over the day, the effects of taking medication on different parts of the day should be studied. As discussed above, the long-term effect of physical activity increase is expected to result in a decrease in morning symptoms. Physical activity should be assessed with objective methods in research, but also in clinical practice. A combination with a questionnaire that evaluates the difficulty to perform physical activity is warranted. With this approach, it becomes more clear whether patients are they limited by symptoms, by physical inactivity or both. A possibility to improve physical activity in patients with high morning symptom scores, is offering physical activity programs in the evening instead of morning/afternoon. If patients suffer from symptoms in the morning and have already made changes in morning routines due to symptoms, it might in our opinion not be effective to stimulate physical activity in the morning. Offering physical activity programs in the evening will potentially result in less interference with daily activities. This can result in more adherence to activity recommendations, also in the post-rehabilitation period. Since physical inactivity is already present in non-severe COPD stages, we recommend to include patients with non-severe COPD in studies as well. We think that physical activity interventions have the potential to slow down disease progression. It is promising to combine interventions to improve morning symptoms as well as physical activity. Examples of interventions are presented in

figure 1. Combining interventions can potentially result in synergistic positive effects, but this needs to be studied in future studies.

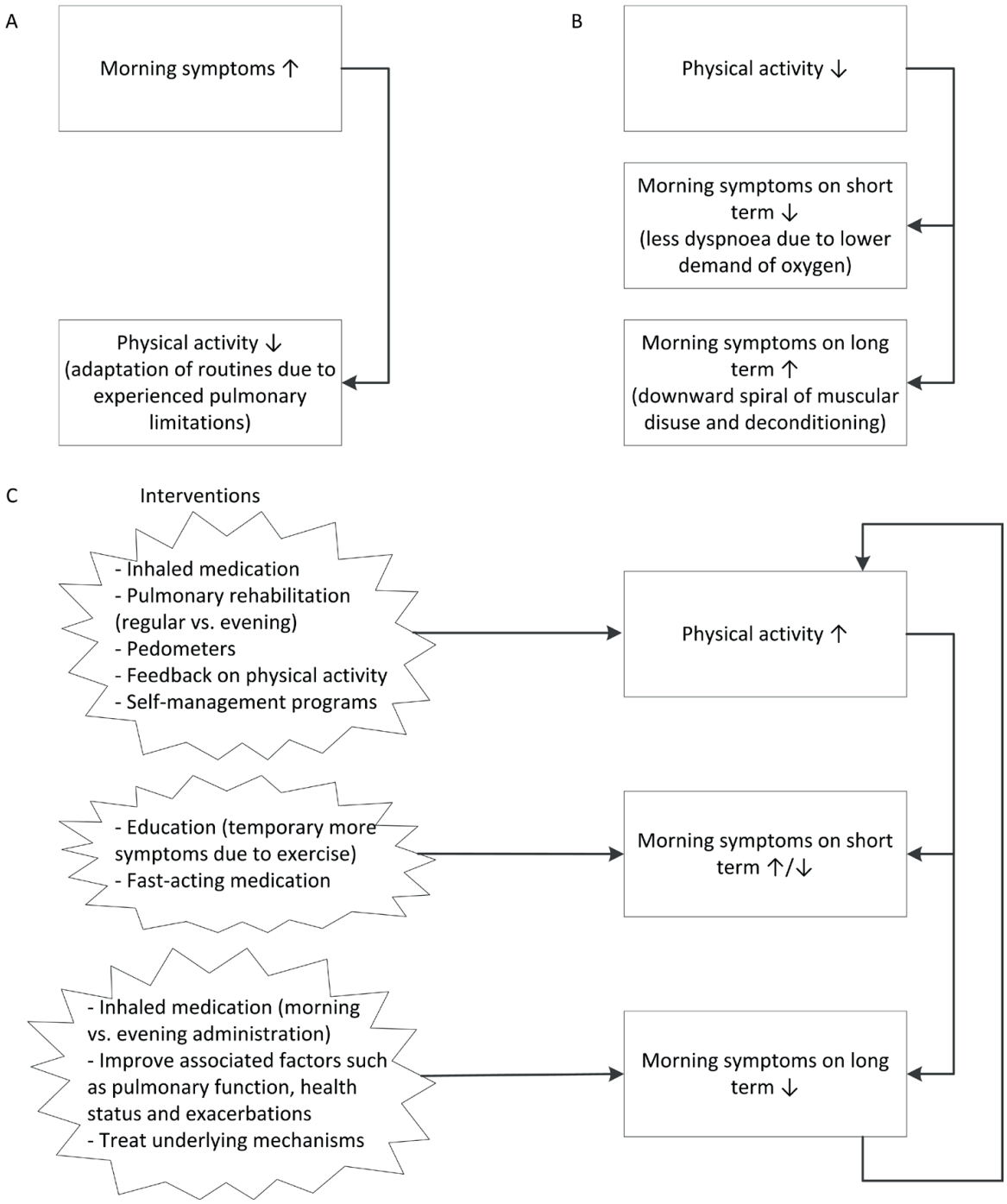

Figure 1. Relation between morning symptoms and physical activity. A) Untreated situation: morning symptoms causes physical inactivity. B) Untreated situation: physical inactivity causes morning symptoms. C) Interventions to increase physical activity and morning symptoms. A combination of interventions might have a synergistic effect.

LIST OF ABBRIVATIONS

COPD: chronic obstructive pulmonary disease
FEV_1: forced expiratory volume in 1 second
IPAQ: international physical activity questionnaire
LUMC: Leiden University Medical Center
MODAS: MOrning symptoms in-Depth observationAl Study
NEO: Netherlands Epidemiology of Obesity
SQUASH: short questionnaire to assess health-enhancing physical activity
TH2: T-helper 2
WHO: World Health Organisation

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Summary

Chapter 1 provided an overview of chronic obstructive pulmonary disease (COPD) in general, morning symptoms in patients with COPD, physical activity in general and physical activity in COPD. The World Health Organisation (WHO) showed in their most recent report on the top ten causes of death that COPD is the third leading cause of death worldwide. There are no curative options for COPD yet. However, COPD is a treatable disease, whereby reduction of symptoms and prevention of acute exacerbations are seen as most important treatment goals. Symptoms can occur during each part of the day, whereby the morning is the most symptomatic part of the day. Exacerbations are defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a sudden worsening of respiratory symptoms that result in additional therapy. COPD can be treated with bronchodilators, inhaled corticosteroids and lifestyle advises such as smoking cessation, exercise training and sufficient physical activity. Physical activity is defined by the WHO as "any bodily movement produced by skeletal muscles that results in energy expenditure." Unfortunately, physical inactivity is common in COPD. Physical inactivity in COPD is related to high mortality rates, lower quality of life, more dyspnoea and more previous exacerbations. Despite the mentioned treatment options, COPD frequently causes disability. More research is needed in factors that are related with poor outcomes in COPD, such as morning symptoms and physical inactivity. The aim of this thesis was to gain more knowledge about morning symptoms and physical activity in COPD in search of novel treatment options.

In **chapter 2**, the results of a systematic review on the current evidence of the association between morning symptoms and physical activity in patients with COPD were shown. Eight studies were included in this review. Across all COPD stages, 37.0 to 90.6% of patients reported a relation between more morning symptoms and lower self-reported physical activity. All included studies used questionnaires to assess physical activity.

Following the results of the systematic review, we designed the MOrning symptoms in-Depth observationAl Study (MODAS) to evaluate the association between morning symptoms, other patient characteristics and objectively measured physical activity. The MODAS was a single center cross-sectional study that was conducted at the Leiden University Medical Center (LUMC). 80 patients with moderate to very severe COPD were included. Morning symptoms were assessed with the PRO-Morning COPD symptoms questionnaire. Patients ranked the severity of dyspnoea, sputum production, chest tightness, wheezing, cough in the morning and limitations due to symptoms in the morning. The total score of the PRO-Morning COPD symptoms questionnaire ranged from 0 to 60. A low scores indicates less morning symptoms than a high score. Physical activity was objectively measured with an accelerometer that was worn on the lower back for seven consecutive days, 24-hour a day. An accelerometer is a device that measures acceleration in different axes. In **chapter 3**, we showed that patients had a mean morning symptom score of 19.7. We demonstrated

that patients with overall more symptomatic COPD have higher morning symptom scores. Therefore, we concluded that morning symptoms should be carefully assessed in addition to general COPD-specific questionnaires measuring symptoms, especially in those with more symptomatic COPD. Furthermore, lower health status, increased anxiety and depression, lower objectively measured physical activity and lower pulmonary function were associated with an increased morning symptom severity. These factors can be potential targets for intervention to improve morning symptoms. In **chapter 4**, we described physical activity patterns during the course of the day. Patients were divided into two groups of comparable size based on their morning symptom score: 41 patients had low a morning symptom score (total morning symptom score <17.0) and 39 patients had a high morning symptom score (total morning symptom score ≥17.0). We showed that patients with low morning symptom scores took more steps in the morning and afternoon than patients with high morning symptom scores. There was no significant difference in number of steps during the evening and night between patients with low and high morning symptoms scores. This was the first study that investigated activity patterns in patients with COPD during the course of the day, while taking morning symptoms into account. However, causality between morning symptoms and physical activity during different parts of the day could not be proven, due to the cross-sectional design of the study. We speculated that physical activity programs in the evening instead of the morning or afternoon might be helpful for COPD patients with morning symptoms, as the evening seems to be the most suitable part of the day for increasing physical activity.

Since physical inactivity is already present in mild and moderate COPD, we focussed in **chapter 5** on physical activity and associated characteristics in non-severe COPD patients. We used baseline data from the Netherlands Epidemiology of Obesity (NEO) study, a large population-based cohort study that was conducted from 2008 to 2012 in the greater area of Leiden, the Netherlands. Patients were included in the analyses if they had physician diagnosed COPD with an International Classification of Primary Care (ICPC) code for COPD (R95) or if patients met our criteria for newly diagnosed COPD. 323 patients were included, of which 77 met the criteria for physician diagnosed COPD and 246 met the criteria for newly diagnosed COPD. We showed that pulmonary function was positively associated with self-reported physical activity in patients with non-severe COPD. The presence of a physician diagnosed COPD and the use of nearly all pulmonary medication were associated with less self-reported physical activity. In this study, we found no association between increased symptoms in the morning and self-reported physical activity. We concluded that prospective intervention studies are needed to determine whether early pharmacological interventions and/or physical activity could slow down COPD progression in non-severe COPD. It is important to include patients with non-severe COPD in studies, because there is room for improvement in this specific patient group.

In **chapter 6**, we evaluated a novel systematic approach for patients with (suspected) asthma and COPD referred to secondary care pulmonology. Patients visited the outpatient clinic of the department of pulmonology at the LUMC. The systematic approach consisted of a predefined systematic diagnostic evaluation. An internet-based self-management support system was a non-obligatory part of the systematic approach. Outcomes were compared to usual care. 125 patients were included in the study, of which 22 (21.4%) were evaluated with the systematic approach. Patients who were evaluated with the systematic approach underwent more diagnostic tests when compared to usual care. There were no differences in the final diagnoses. This suggests that only a part of the diagnostic tests that were included in the systematic approach are regularly needed to make specific diagnosis. More lifestyle advice, symptom scores and individual care plans were electronically recorded. Furthermore, more patients were referred back to primary care when compared to usual care. We showed in our study that it is possible to use a systematic approach in secondary care pulmonology and that this stimulates physicians to record lifestyle advice, symptoms and individual care plans. Further research is needed to evaluate the impact of this systematic approach on disease control, quality of life, lifestyle changes and costs.

In **chapter 7**, we provided a general summary, we discussed hypotheses based on the studies in this thesis and gave directions for future research and clinical practice. We started the discussion with methodological considerations. We concluded that different study populations, morning symptom questionnaires, tools to assess physical activity and study designs contributed to differences in study outcomes. Thereafter, we discussed the question whether morning symptoms cause physical inactivity, or is it the other way around. There is a relation between morning symptoms and physical activity as shown in the MODAS and previous studies. We believe that it is twofold; morning symptoms can cause physical inactivity, but physical inactivity can cause morning symptoms as well. Yet, it is not possible to prove causality between morning symptoms and physical activity since prospective studies are lacking. Therefore, we have to search for (a combination of) interventions that target morning symptoms as well physical activity. Then, we discussed the question whether morning symptoms are a distinct phenotype in COPD. A phenotype in COPD has been defined as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes." We concluded that morning symptoms are related to other factors that are associated with poor outcomes in COPD. However, it is not possible yet to state that morning symptoms are a distinct phenotype in COPD since we should first know the effects of morning symptoms on long term. Thereafter, we discussed the question whether pulmonologists need a systematic approach to diagnose obstructive lung diseases and improve treatment plans. We concluded that a systematic approach is not necessary to make specific diagnoses, but it can be used as a tool to pay attention for patient characteristics that can be overlooked

in clinical practice. In this thesis we argued for the implementation of the assessment of morning symptoms and objectively measured physical activity in systematic approaches. The studies in this thesis highlighted the importance of morning symptoms and physical inactivity in patients with COPD. With our research, we gained new insights in morning symptoms and physical activity in COPD. These factors can be used as targets for therapy in future interventional studies. Combining interventions can potentially result in even greater positive effects, but this needs also to be studied in future studies.

LIST OF ABBREVIATIONS AND EXPLANATIONS

Accelerometer: a device that measures acceleration in different axes
COPD: chronic obstructive pulmonary disease
GOLD: Global Initiative for Chronic Obstructive Lung Disease
ICPC: International Classification of Primary Care
LUMC: Leiden University Medical Center
MODAS: MOrning symptoms in-Depth observationAl Study
NEO study: Netherlands Epidemiology of Obesity study
Phenotype: "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes"
Physical activity: "any bodily movement produced by skeletal muscles that results in energy expenditure"
WHO: World Health Organisation

ADDENDUM

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 geeft een overzicht van chronische obstructieve longziekte (COPD) in het algemeen en longklachten in de ochtend bij mensen met COPD. Daarnaast geeft dit hoofdstuk een samenvatting over lichamelijke activiteit in het algemeen en lichamelijke activiteit bij mensen met COPD. COPD is op dit moment wereldwijd doodsoorzaak nummer drie (Bron: Wereldgezondheidsorganisatie). Heden ontbreken er behandelingen die COPD genezen. De belangrijkste doelen bij de behandeling van COPD zijn het verminderen van longklachten en het voorkomen van longaanvallen. Longklachten kunnen op ieder moment van de dag voorkomen, maar de meeste mensen met COPD ervaren de ochtend als meest problematische periode van de dag. Een longaanval is een plotselinge verslechtering van longklachten waar aanvullende behandeling voor nodig is (Bron: richtlijn Global Initiative for Chronic Obstructive Lung Disease 2018). COPD kan behandeld worden met luchtwegverwijders, ontstekingsremmers en lifestyleadviezen. Voorbeelden van lifestyleadviezen zijn stoppen met roken, spier- en botversterkende oefeningen en lichamelijke activiteit. Lichamelijke activiteit wordt gedefinieerd als "iedere beweging van het lichaam, opgewekt door skeletspieren, die energie verbruikt" (Bron: Wereldgezondheidsorganisatie). Helaas komt lichamelijke inactiviteit vaak voor bij mensen met COPD. Lichamelijke activiteit bij mensen met COPD heeft een relatie met hogere kans op sterfte, lagere kwaliteit van leven, meer benauwdheidsklachten en meer longaanvallen. Ondanks de hierboven genoemde behandelopties, is COPD verantwoordelijk voor beperkingen in het dagelijks leven. Om de ontwikkeling van nieuwe behandelopties aan te moedigen, is er meer onderzoek noodzakelijk naar negatieve factoren bij COPD, zoals longklachten in de ochtend en lichamelijke inactiviteit. Het doel van dit proefschrift was om meer inzicht te krijgen in longklachten in de ochtend en lichamelijke activiteit.

Hoofdstuk 2 richt zich op bestaande literatuur die de relatie tussen longklachten in de ochtend en lichamelijke activiteit bij mensen met COPD beschrijft. Acht gepubliceerde onderzoeken werden geïncludeerd. Alle ziektestadia waren vertegenwoordigd. Er werd geconcludeerd er bij 37.0 tot 90.6% van de mensen met COPD een relatie was tussen het hebben van meer longklachten in de ochtend en minder zelf-gerapporteerde lichamelijke activiteit. Als kanttekening werd geplaatst dat alle onderzoeken die gebruikt werden om tot deze conclusie te komen, gebruik maakten van vragenlijsten om lichamelijke activiteit te meten en er hadden geen objectieve metingen plaatsgevonden.

In reactie hierop, werd een onderzoek opgezet met de naam "MOrning symptoms in-Depth observationAl Study" (MODAS), om de relatie tussen longklachten in de ochtend, andere patiëntkenmerken en objectief gemeten lichamelijke activiteit bij mensen met COPD te bestuderen. De MODAS werd uitgevoerd in het Leids Universitair Medisch Centrum

(LUMC). 80 mensen met matig tot zeer ernstig COPD werden geïncludeerd. Longklachten in de ochtend werden gemeten met een vragenlijst, de PRO-Morning COPD symptoms questionnaire. Met deze vragenlijst konden patiënten de ernst van de benauwdheid, de slijmproductie, het strakke gevoel om de borst, de piepende ademhaling, het hoesten in de ochtend en de beperkingen door deze symptomen scoren. De totale score was tussen 0 en 60. Hoe lager de score, des te minder klachten heeft de patiënt. Elke patiënt bezocht één dag het LUMC. Daarna werd er 24 uur per dag een accelerometer op de onderrug gedragen voor zeven aaneengesloten dagen. Accelerometers zijn apparaten met bewegingssensoren die bewegingen in meerdere richtingen registreren. In **hoofdstuk 3** worden de uitkomsten van dit onderzoek beschreven. Patiënten hadden een gemiddelde score van 19.7 op de PRO-Morning COPD symptoms questionnaire. Er werd vastgesteld dat patiënten met ernstiger COPD, ook ernstigere longklachten in de ochtend hebben. We konden concluderen dat het uitvragen van longklachten in de ochtend belangrijk is, in het bijzonder bij patiënten met ernstiger COPD. Daarnaast werd er een relatie gevonden tussen een lagere COPD-gerelateerde gezondheidsstatus, hogere algemene longklachtenscores, hogere angst- en depressiescores, minder lichamelijke activiteit die objectief gemeten is, slechtere longfunctie en ernstigere longklachten in de ochtend. Deze factoren zouden we als behandeldoelen kunnen zien om indirect longklachten in de ochtend te verbeteren. In **hoofdstuk 4** worden activiteitenpatronen gedurende de dag van de patiënten die deelnamen aan de MODAS beschreven. De totale groep werd in twee groepen verdeeld van ongeveer gelijke grootte, op basis van de ernst van de longklachten in de ochtend. 41 patiënten hadden weinig longklachten in de ochtend (totale score op de PRO-Morning COPD symptoms score <17.0) en 39 patiënten hadden veel longklachten in de ochtend (totale score op de PRO-Morning COPD symptoms score ≥17.0). Patiënten met veel longklachten in de ochtend, zetten minder stappen in de ochtend en in de middag dan patiënten met weinig longklachten in de ochtend. Er is geen relevant verschil waargenomen tussen de twee groepen in de hoeveelheid stappen die gezet werden in de avond en nacht. Dit was het eerste onderzoek dat gedaan is naar activiteitenpatronen gedurende de dag waarbij de ernst van de longklachten in de ochtend in acht werden genomen. Helaas kunnen we met dit onderzoek niet zeggen of de longklachten in de ochtend de oorzaak is van de verminderde lichamelijke activiteit in de ochtend en de middag of dat het juist het gevolg is; daar is vervolgonderzoek voor nodig. We opperden dat activiteitenprogramma's wellicht beter in de avond plaats kunnen vinden dan in de ochtend of middag, omdat het lijkt dat er in de avond ruimte is voor toename van lichamelijke activiteit.

Lichamelijke inactiviteit is geen kenmerk voor alleen ernstig COPD; ook bij patiënten met mild en matig COPD is er sprake van vermindering in lichamelijke activiteit. In **hoofdstuk 5** wordt de relatie beschreven tussen patiëntkenmerken en lichamelijke activiteit bij patiënten met niet-ernstig COPD. Hiervoor is gebruikt gemaakt van de basisgegevens van

mensen die deelnamen aan het "Netherlands Epidemiology of Obesity" (NEO) onderzoek. Dit is een grootschalig onderzoek dat van 2008 tot 2012 is gedaan bij vrijwilligers uit de regio van Leiden. In de analyses werd er onderscheid gemaakt tussen mensen die de diagnose COPD door een arts hadden gekregen waarbij de code voor COPD (R95) ook geregistreerd stond in het elektronische dossier; en mensen die voldeden aan onze criteria voor nieuw gediagnosticeerd COPD. In totaal werden 323 patiënten geïncludeerd waarvan 77 patiënten de diagnose COPD door een arts hadden gekregen en 246 patiënten voldeden aan de criteria voor nieuw gediagnosticeerd COPD. We vonden een relatie tussen het hebben van een betere longfunctie en meer lichamelijke activiteit. Daarnaast werd er een relatie gevonden tussen het hebben van COPD dat door een arts gediagnosticeerd was, het gebruik van bijna alle longmedicijnen en verminderde lichamelijke activiteit. Er was in deze groep geen relatie tussen lichamelijke activiteit en het hebben van toename van longklachten in de ochtend. We concludeerden dat vervolgonderzoeken noodzakelijk zijn om het effect van vroege behandelingen met medicatie en/of lichamelijke activiteit op achteruitgang van COPD in kaart te brengen. Het huidige onderzoek benadrukt dat het ook belangrijk is om onderzoek te doen bij mensen met niet-ernstig COPD. In deze groep is het COPD nog niet vergevorderd en is er ruimte voor verbetering.

In **hoofdstuk 6** wordt de evaluatie van een nieuw zorgpad beschreven, waarbij patiënten met (een verdenking op) astma en/of COPD op een systematische wijze werden gezien op de longpolikliniek van het LUMC. Een zorgpad is een complexe interventie op de gemeenschappelijke besluitvorming en organisatie van zorgprocessen te verwezenlijken voor een specifieke groep van patiënten gedurende een gedefinieerd tijdskader (Bron: European Pathway Association). Dit betekende voor de patiënten in het LUMC dat ze allemaal dezelfde vooraf bepaalde aanvullende onderzoeken ondergingen. Daarnaast kregen patiënten de mogelijkheid om via internet gebruik te maken van een elektronisch hulpprogramma om zelfredzaamheid in het kader van astma en COPD te vergroten. De uitkomsten werden vergeleken met "gewone" zorg. 125 patiënten werden geïncludeerd, waarvan 22 (21.4%) werden gezien volgens het nieuwe zorgpad. Patiënten die volgens het zorgpad gezien werden, ondergingen meer aanvullende onderzoeken in vergelijking met patiënten die niet volgens het zorgpad gezien werden en "gewone" zorg kregen. Er werden geen verschillen gevonden in de gestelde diagnoses. Dit suggereert dat niet alle testen die opgenomen zijn in het zorgpad, ook daadwerkelijk nodig zijn om een goede diagnose te stellen. Echter, werden er meer lifestyleadviezen, meer symptoomscores en meer individuele zorgplannen elektronisch gedocumenteerd bij patiënten die volgens het zorgpad gezien werden in vergelijking met "gewone" zorg. Uiteindelijk werden er meer patiënten terugverwezen naar de huisarts. Een zorgpad stimuleert longartsen om lifestyleadviezen, symptoomscores en individuele zorgplannen elektronisch te registreren. Het zorgpad kan er voor zorgen dat meer mensen worden terugverwezen naar de huisarts. We

hebben met dit onderzoek laten zien dat het mogelijk is om een zorgpad voor astma en COPD te gebruiken in de dagelijkse praktijk. Meer onderzoek is nodig om de effecten van het zorgpad op andere uitkomstparameters als kwaliteit van leven, lifestyleveranderingen en kosten te evalueren.

In **hoofdstuk 7** worden een algemene samenvatting, hypotheses gebaseerd op de studies uit dit proefschrift en richtingen voor vervolgonderzoek en voor de klinische praktijk gegeven. De discussie startte met methodologische overwegingen. We concludeerden dat verschillende studiepopulaties, vragenlijsten om longklachten in de ochtend te evalueren, methoden om lichamelijke activiteit te meten en de opzet van de studie hebben bijgedragen aan verschillen in uitkomsten. Vervolgens bediscussieerden we de stelling dat longklachten in de ochtend lichamelijk inactiviteit veroorzaken, of dat het juist de andere kant op werkt: dat lichamelijke inactiviteit longklachten in de ochtend veroorzaakt. In de MODAS en in andere onderzoeken is aangetoond dat er een relatie is tussen symptomen in de ochtend en lichamelijke activiteit. Er valt echter met deze onderzoeken niet aan te tonen of longklachten in de ochtend lichamelijk inactiviteit veroorzaken, of dat het juist de andere kant op werkt. We denken het inderdaad beide kanten op werkt. Daarom moeten we gaan zoeken naar (een combinatie van) behandelingen die zowel longklachten in de ochtend, als lichamelijke activiteit verbetert. Daarna bediscussieerden we de stelling dat het hebben van longklachten in de ochtend een fenotype is in COPD. Een fenotype is een enkele of combinatie van ziekte eigenschappen die verschillen beschrijven tussen individuen met dezelfde ziekte, die een relatie hebben met klinisch relevante uitkomsten. We concluderen dat er een relatie is tussen het hebben van longklachten in de ochtend en andere factoren die negatieve invloed hebben op COPD. Echter, kunnen we nog niet concluderen dat het hebben van longklachten in de ochtend een fenotype is in COPD, omdat we het effect op de lange termijn niet weten. Vervolgens bediscussieerden we de stelling dat longartsen een systematische werkwijze nodig hebben om specifieke diagnoses te stellen en betere behandelplannen te maken. We concludeerden dat longartsen geen systematische werkwijze nodig hadden om specifieke diagnoses te stellen. Wel kan er gebruik worden gemaakt van een systematische werkwijze om meer aandacht te hebben voor specifieke patiëntkenmerken die anders in de dagelijkse praktijk over het hoofd gezien worden. In dit proefschrift pleiten we voor het invoegen van vragenlijsten die gaan over longklachten in de ochtend en het objectief meten van lichamelijke activiteit. De onderzoeken beschreven in dit proefschrift, hebben bijgedragen aan het onderstrepen van het belang van longklachten in de ochtend en lichamelijke inactiviteit bij mensen met COPD. Met ons onderzoek hebben we nieuwe inzichten gegeven in longklachten in de ochtend en lichamelijke inactiviteit. Deze factoren kunnen worden beschouwd als potentiele behandelopties om negatieve factoren in COPD positief te beïnvloeden. Mogelijk kan

een combinatie van behandelingen resulteren in een elkaar versterkend effect. De effecten zullen moeten worden onderzocht in vervolgonderzoeken.

AFKORTINGEN EN TOELICHTING TERMINOLOGIE

Accelerometer: Dit is een apparaat met bewegingssensoren die bewegingen in meerdere richtingen registreert
COPD: chronische obstructieve longziekte
Fenotype: een enkele of combinatie van ziekte eigenschappen die verschillen beschrijven tussen individuen met dezelfde ziekte, die een relatie hebben met klinisch relevante uitkomsten
Lichamelijke activiteit: iedere beweging van het lichaam, opgewekt door skeletspieren, die energie verbruikt
LUMC: Leids Universitair Medisch Centrum
MODAS: MOrning symptoms in-Depth observationAl Study
NEO onderzoek: Netherlands Epidemiology of Obesity onderzoek
Zorgpad: een complexe interventie op de gemeenschappelijke besluitvorming en organisatie van zorgprocessen te verwezenlijken voor een specifieke groep van patiënten gedurende een gedefinieerd tijdskader

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CURRICULUM VITAE

Amanda Rosanne van Buul was born on February 23th in 1988 in Spijkenisse, the Netherlands. In 2006 she graduated from the Gymnasium at Comenius College, Capelle aan den IJssel, the Netherlands. Subsequently, she began medical school at the Erasmus University in Rotterdam. After receiving her medical degree in December 2012 (*cum laude*), she started as a resident Internal Medicine at the Albert Schweitzer Ziekenhuis in Dordrecht. In November 2014 she started working at the Leiden University Medical Center as a resident in the Department of Pulmonology. In May 2015 she started her PhD project at the Department of Pulmonology, under supervision of prof. dr. C. Taube, prof. dr. N.H. Chavannes and dr. M.J. Kasteleyn. The results of this PhD project are described in this thesis. In January 2019 she started residency training at Reinier de Graaf ziekenhuis in Delft followed by specialty training in Pulmonology in the Leiden University Medical Center.

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