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

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

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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).

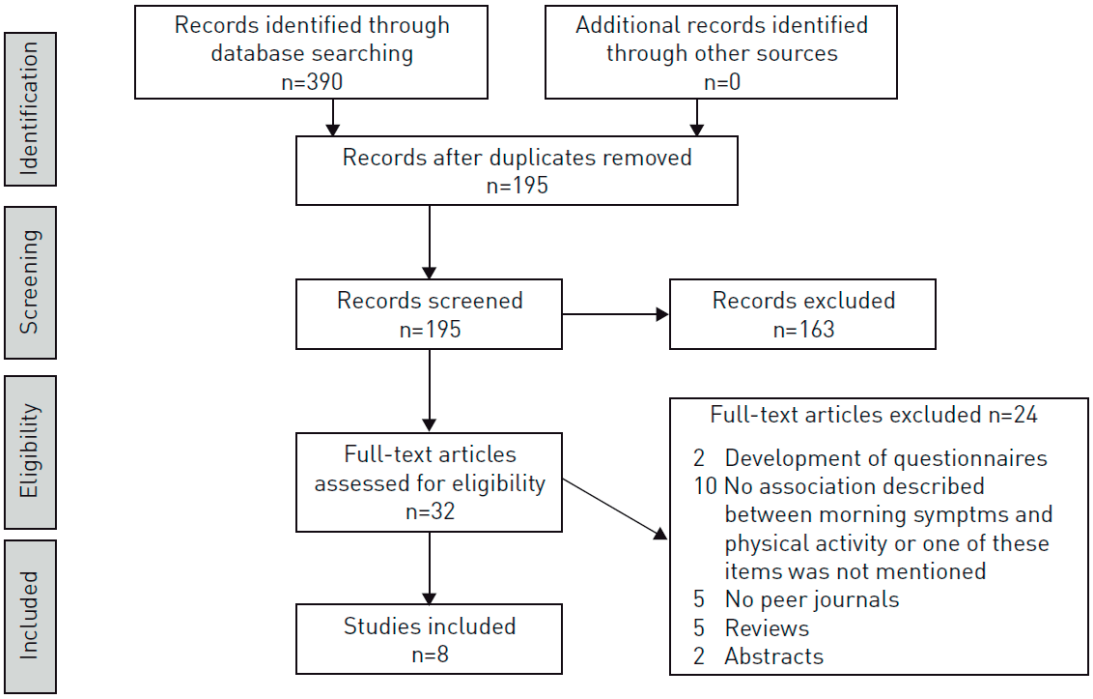

Figure 1 Study flow diagram with the use of the official PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart.

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.

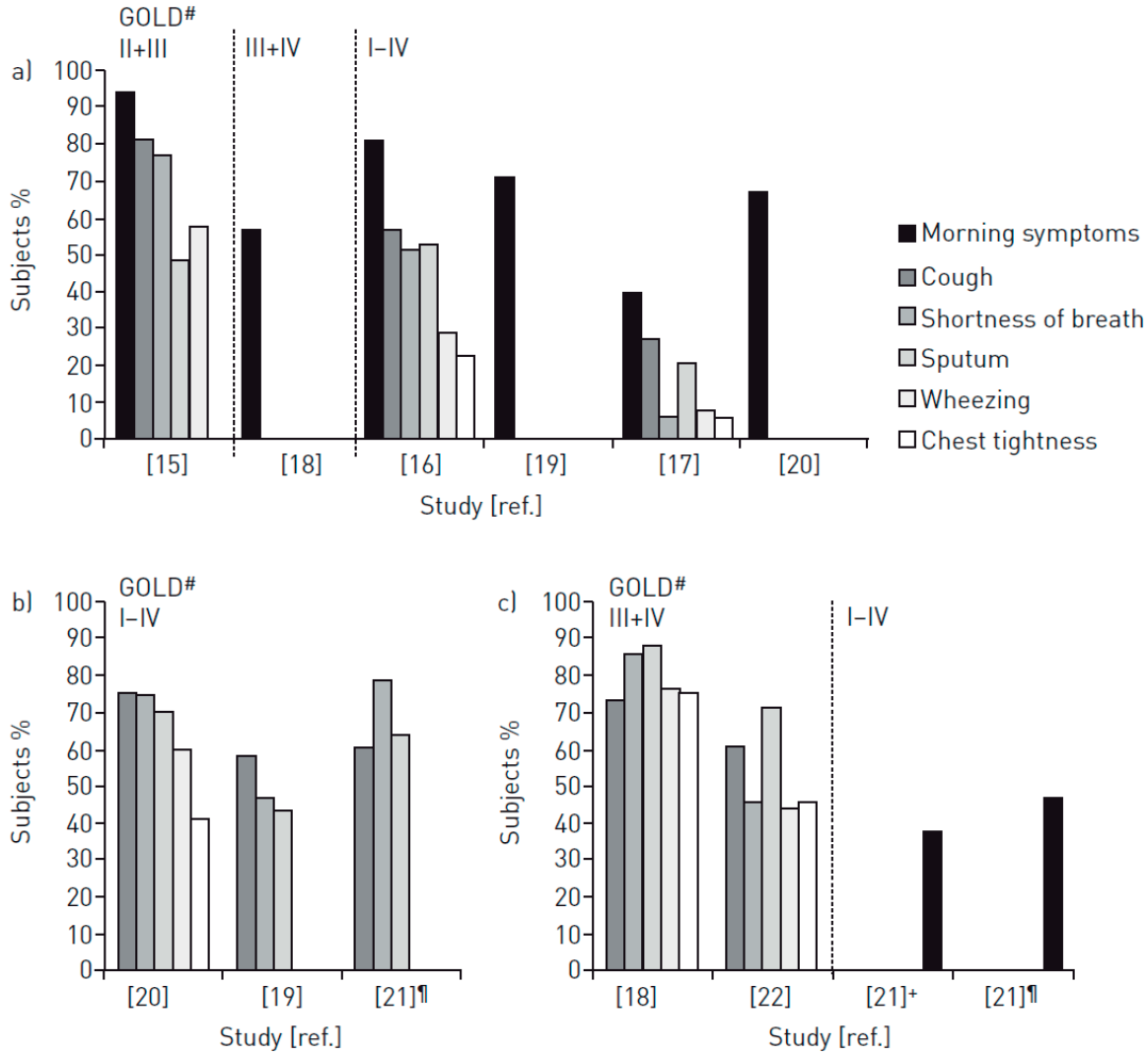

Figure 2 Occurrence of morning symptoms. a) In all studied chronic obstructive pulmonary disease (COPD) patients. b) Occurrence of different morning symptoms in COPD patients experiencing symptoms. c) Symptomatic COPD patients who report the morning as worst time of the day for that symptom (results 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