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

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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.

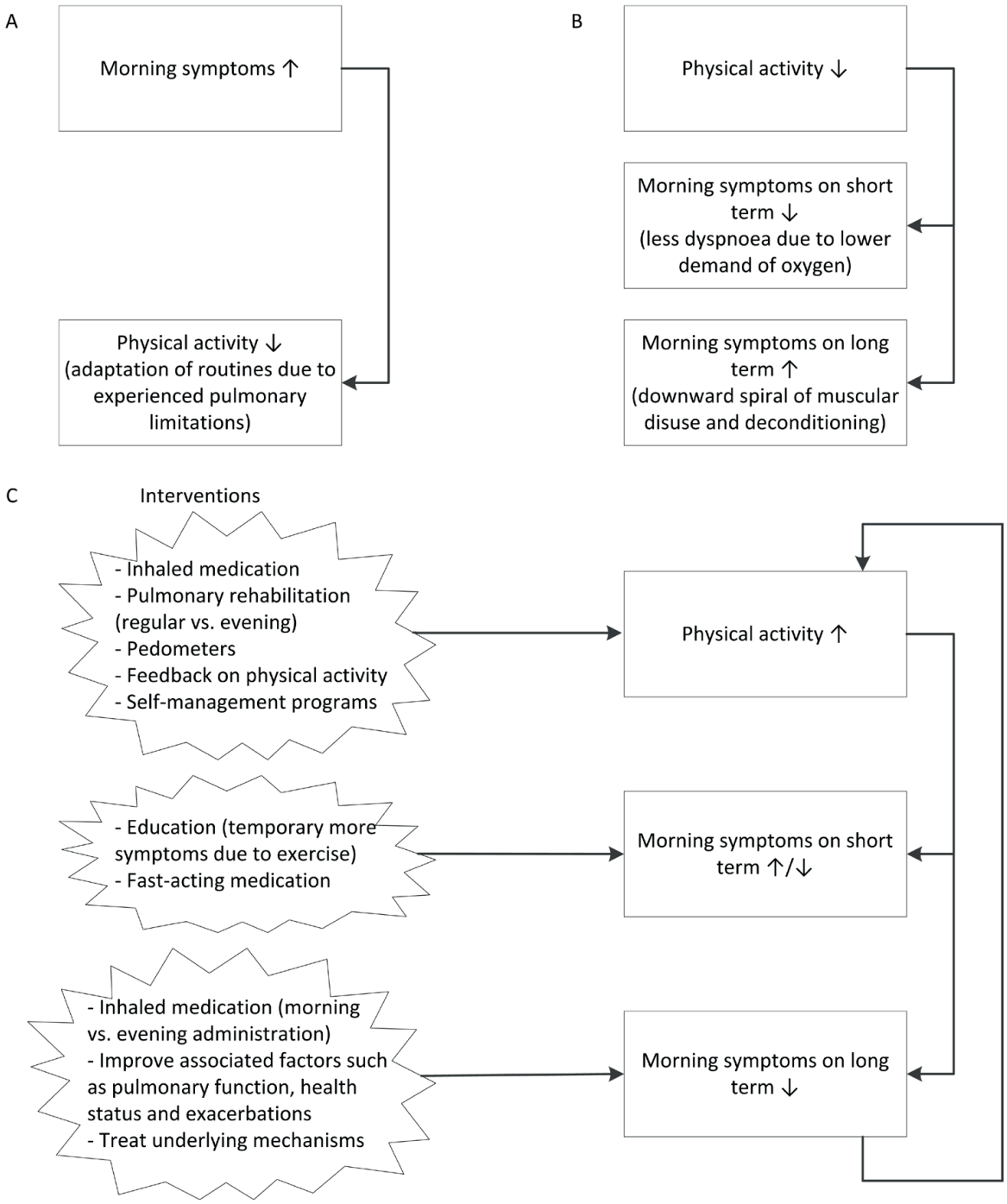

Figure 1. Relation between morning symptoms and physical activity. A) Untreated situation: morning symptoms causes physical inactivity. B) Untreated situation: physical inactivity causes morning symptoms. C) Interventions to increase physical activity and morning symptoms. A combination of interventions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