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Research context

The present master thesis fits in the framework of rehabilitation of cardiopulmonary and internal diseases (CRI). This study area has a wide variety of diseases such as obesity, chronic obstructive pulmonary disease, type II diabetes and cancer. The CRI research cluster of the REVAL Rehabilitation Research Center investigates the effect of exercise training interventions on those diseases and tries to optimize them. They also investigate the underlying mechanisms of exercise training interventions. The CRI research cluster works in close collaboration with CIRO Rehabilitation center at Hornerheide (The Netherlands, Prof. dr. Martijn Spruit) and other laboratories and universities. The focus will be on patients with chronic obstructive pulmonary disease. These people can experience exacerbations, which is an acute worsening of the disease and its symptoms. The effects of an exacerbation have already been investigated in this population. There is however a scarcity of studies that investigate the impact on factors associated with frailty. It is known that exacerbations of chronic obstructive pulmonary disease have a negative impact on patients' health status. (https://www.uhasselt.be/Documents/BIOMED/Documenten%20Reval/BIOMED_CRI_EN.pdf).

The aim of the master thesis is to investigate the association of an acute exacerbation with functional parameters related to frailty in people with chronic obstructive pulmonary disease (COPD). Identifying the impact of an AECOPD on the functional status could facilitate a more targeted approach during rehabilitation.

The two master students (B.R. and Ö.S.) were enrolled in an already existing study where they had to investigate a part of the main research question. The research design had already been selected by copromotor Dr. C. Burtin. The main research question was provided by the copromotor. The students were allowed to finetune this question and define what they wanted to investigate. The different tests that were used in the study were introduced by the copromotor. Determining the instructions and the exact way the tests needed to be performed was done in consultation with the students. Patient recruitment was done by pneumologist Dr. M. Daenen, who screened his patients at Ziekenhuis Oost-Limburg for eligibility.

After this screening, patients were informed further by Dr. C. Burtin or one of the master students. Both students were trained in 2017 to adequately perform the tests. Both of them helped with performing the tests and acquiring the data for the study. The initial two test sessions were done in cooperation with the copromotor. After these sessions, the master students were allowed to perform these tests alone. The selection of statistical models and performing the data analysis was done by the master students and was checked afterwards by the copromotor.

This master thesis was written using the central format. The writing was performed together by the master students, who both had an equal contribution to the process. The promotor and copromotor provided feedback and suggestions that were taken into account during the writing process.

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1. Abstract

Background: COPD patients have a decline in health status and a high incidence of frailty. Evidence indicates that exacerbations (AECOPD) lead to a further decline in health status, which could lead to increasing frailty.

Objectives: The aims of this study were to investigate the association of an AECOPD in the previous year with functional parameters related to frailty.

Participants: Stable and AECOPD patients were compared in a cross-sectional design. The exacerbations were retrospectively investigated.

Measurements: The CIS Fatigue Scale, Actigraph GT3X accelerometer, BIA, Microfet, 4MGS, 5STS and the SPPB were used to respectively measure fatigue levels, physical activity, FFM, Quadriceps muscle force, gait speed, sit-to-stand and functional status. The 6MWD and handgrip strength were also recorded.

Results: A total of 24 participants were included in the final cohort. The mean age (± SD) was 65.63 ± 8.29 years and 54% was male. Of the 15 patients who experienced one or more exacerbations in the previous year, four patients required hospitalization. The differences between AECOPD and stable patients, after correction for confounders, were not significant for all of the outcome measures. A trend towards significant scores can be noted for the 4MGS (p= 0.088), 5STS (p= 0.079), QMF (p= 0.108), and physical activity levels (p= 0.084).

Conclusion: COPD patients who experienced AECOPD in the preceding year, although not significantly different, performed worse on functional parameters associated with frailty. The findings of the current study showed similarities with other literature, which means the results could be representative for the target population. Future research is needed with a comparison of functional status between pre- and post-AECOPD measurements.

2. Introduction

GOLD defines chronic obstructive pulmonary disease (COPD) as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease and parenchymal destruction, the relative contributions of which vary from person to person" (GOLD, 2018). The disease is characterized by high morbidity and mortality rates (Caballero et al., 2008; Koblizek et al., 2013; Minino, Murphy, Xu, & Kochanek, 2011) and high economic costs (Criner et al., 2015). An exacerbation, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), is 'an acute worsening of respiratory symptoms that result in additional therapy' (GOLD, 2018). Exacerbations of COPD (AECOPD) result in an increase in economic costs, morbidity and mortality rates (Andersson et al., 2002; Anzueto, 2010; Carr, Goldstein, & Brooks, 2007; Chhabra & Dash, 2014; Friedman & Hilleman, 2001; Miravitlles, Jardim, Zitto, Rodrigues, & Lopez, 2003; Miravitlles, Murio, Guerrero, & Gisbert, 2002; Miravitlles et al., 2014; Niewoehner, 2006; Pradan, Ferreira, & Postolache, 2013; Qaseem et al., 2011; Rennard et al., 2013; Suissa, Dell'Aniello, & Ernst, 2012).

Aside from impaired respiratory mechanics, COPD patients are characterized with a decline in muscle strength, physical activity and exercise capacity (Anzueto, 2010; Gimeno-Santos et al., 2014; Hopkinson et al., 2007; Pitta et al., 2005; Troosters, Sciurba, et al., 2010). Evidence indicates that exacerbations result in a further decline in physical activity, muscle strength and exercise capacity (Anzueto, 2010; Borges & Carvalho, 2012; Burtin, Decramer, Gosselink, Janssens, & Troosters, 2011; Chhabra & Dash, 2014; Garcia-Aymerich, Lange, Benet, Schnohr, & Anto, 2006; Pitta et al., 2006; Spruit et al., 2003). This could be due to an increase in systemic inflammation (Burtin et al., 2011; Hurst et al., 2006; Markoulaki et al., 2011; Mercer et al., 2005; Wedzicha et al., 2000; Wouters, Groenewegen, Dentener, & Vernooy, 2007), a decrease in energy levels (Burtin et al., 2011; Vermeeren, Schols, & Wouters, 1997), a decrease in anabolic hormone levels (Burtin et al., 2011; Kamischke et al., 1998; Karadag, Ozcan, Karul, Yilmaz, & Cildag, 2009; Van Vliet et al., 2005) and/or other pathways of catabolism, apoptosis and mitochondrial chains (Crul et al., 2010). Other mechanisms influencing a decline in physical fitness parameters could be impaired respiratory mechanics, the state of being bedridden, influence of medication and fear.

Frailty is the state of increased vulnerability caused by disabilities associated with aging, leading to an increased risk for worse outcomes, including hospitalization and death (Xue, 2011). According to Yohannes et al., COPD patients become progressively inactive (Valenza et al., 2016; Yohannes, 2001). The study of Valenza et al. and Lahousse et al., investigated frailty in COPD patients by using the modified frailty index by Fried et al., which categorizes older adults as frail when three or more of the following components are present: decreased handgrip strength (adjusted for Body Mass Index (BMI)), weight loss, exhaustion (energy level), slow walking speed, and low physical activity levels (Fried et al., 2001; Lahousse et al., 2016; Valenza et al., 2016). The study of Valenza et al. used the same criteria except for slow walking speed, which was replaced with functional limitation evaluated by the chair stand test (Valenza et al., 2016). According to Park et al., the prevalence of frailty in COPD patients is 57.8% (Park, Richardson, Holleman, & Larson, 2013; Valenza et al., 2016). The risk of mortality is three times higher for frail elderly COPD patients compared to non-frail elderly COPD patients (Lahousse et al., 2016).
The 4m gait speed (4MGS) is a marker for frailty and is associated with an increased risk for hospitalization and disability in community-dwelling elderly (Abellan van Kan et al., 2009; Kon et al., 2015).

Dyspnea and fatigue, which play a major role in the functional limitation of COPD patients, could lead to increasing frailty (Valenza et al., 2016; Yohannes, 2001). Low levels of physical activity, fatigue, muscle strength and mass, mobility limitations, a decrease in gait speed and balance, which are components of frailty, could be worse after an exacerbation (Aaron et al., 2012; Halpin et al., 2012; Valenza et al., 2016). COPD patients with exacerbations could land in a vicious circle of impairment and inactivity, which could lead to increasing frailty (Valenza et al., 2016). Lahousse et al. reported that severe airflow limitation, dyspnea, and frequent exacerbations lead to a higher frailty prevalence (Lahousse et al., 2016).

Most studies investigating the effects of an exacerbation in patients with COPD, investigate the effect on physical fitness levels and lung function. Studies investigating the association of an AECOPD with functional parameters related to frailty are scarce. The aim of this study is to evaluate the association of previous exacerbations on factors associated with frailty. Our hypothesis is that patients who experienced exacerbations will have worse scores on parameters associated with frailty.

3. Methods

3.1. Study design

The study has a cross-sectional design where patients who experienced an AECOPD in the previous year are compared to stable COPD patients. The exacerbation events were recorded retrospectively. Measurements were done after the patients had a consultation with their pneumologist and took approximately 45 minutes - 1 hour. Approval of the study (B371201732540) was given by the ethical committee of Ziekenhuis Oost-Limburg and the University of Hasselt on 17/07/2017.

3.2. Participants

The participants were recruited at Ziekenhuis Oost-Limburg and were initially screened to check if they were eligible for the study. Eligible patients were then further informed by the researchers after which the written informed consent was signed.

The following inclusion criteria were used: patients needed to have a COPD diagnosis (including post-bronchodilator FEV1/FVC < 0.7), had to be over 40 years of age and required to have signed the written informed consent. Patients with other airway diseases were excluded from the study. Patients were divided into two groups, the first group consisting of patients who had not experienced an exacerbation in the previous year (stable) and the second group consisting of patients who had experienced one or more exacerbations in the previous year (AECOPD). Patients were included in the AECOPD group if they were hospitalized for an AECOPD or if they were clinically diagnosed with an exacerbation in the previous year.

3.3. Procedure

The primary outcome measures are the functional status, muscle strength, daily physical activity, fatigue, and weight change. The secondary outcome measures are the functional exercise capacity and body composition.

The functional status was assessed by using the Short Physical Performance Battery (SPPB). It is a valid tool for assessing mobility limitations in patients with COPD which consists of three test items that are each scored on a 4 point ordinal scale (Bernabeu-Mora et al., 2015). The test has a maximum score of 12 and divides functional status in three categories, i.e. >9; 4-9; and <3 (Guralnik et al., 2000). The test items are a 4MGS, five-repetition sit-to-stand test (5STS) and a balance test. For the 4MGS the patient was instructed to walk at his or her normal and comfortable walking speed (Kon et al., 2013).

No start signal was given for this test, instead the patient was able to start walking when they were ready. The timer was started when the patient started moving. The timer was stopped when the first foot of the patient completely crossed the 4m line. For the 5STS the patient needed to stand up and sit down five times, as fast as possible, with their arms across their chest. It was emphasized that they were required to stand fully erect when standing up. The balance test consisted of three positions which the patients had to try to hold for ten seconds each. These positions were: with their feet together, a semi tandem position and a tandem position. The different positions were shown by the researcher, so that the patient could reproduce them. The scores of the different items were added up to provide a total score on the SPPB.

Muscle strength was assessed by using two measures. The isometric handgrip strength (HGS) was measured by a hand held dynamometer (Jamar, Preston, MI, USA). Patients were seated and had to keep their elbow at 90° of elbow flexion while performing the test. The isometric strength of the quadriceps muscle was measured by another hand held dynamometer (Microfet, Biometrics, NL). Patients were seated on a treatment table and had to lay their hands on their thighs to avoid compensations. The patients were instructed to progressively contract the quadriceps muscle in three steps, the third step being a maximal contraction (make test). During both strength tests, the patients were motivated by the researcher in order to achieve a maximal contraction.

Daily physical activity was measured with the Actigraph GT3X accelerometer (Actigraph LLC Pensacola, FL, USA). Patients wore this device continuously for a whole week, except when bathing and showering. This accelerometer is a valid test for measuring physical activity in patients with COPD (Rabinovich et al., 2013).

Body composition was assessed by using a bioelectrical impedance measurement (BIA) (Bodystat 1500, EuroMedix, Belgium). It has been shown that BIA measurements have a good correlation with the DEXA-scan for measuring fat-free mass (FFM) in the elderly population (Ramel, Geirsdottir Og Fau - Arnarson, Arnarson A Fau - Thorsdottir, & Thorsdottir, 2011). This device also calculated the BMI.

Weight change was assessed by consulting the medical files at Ziekenhuis Oost-Limburg. Data from the previous year or previous two years were used.

The functional exercise capacity was assessed by using the six minute walking distance (6MWD). The test was performed in an empty hallway, where two cones were used to mark a length of 30m. Patients were instructed to walk as far as possible within a six minute time period. Patients wore a pulse oximeter to monitor the oxygen saturation throughout the whole test. Patients were instructed to stop the test when the saturation dropped below 85%. The motivation by the researcher was standardized for this test. After each minute, the patients were informed about how much time was remaining. In addition to that, they were told that they were doing well.

Patients were also asked to fill out two questionnaires. Fatigue was assessed by using the Checklist Individual Strength (CIS) – subscale fatigue. This subscale consists of eight questions that have to be rated on a seven point ordinal scale. With the maximum possible score being 56, the following cut off points are used: <27/56 is considered normal, >27/56 indicating mild fatigue levels and >37/56 indicating severe fatigue levels (Goertz et al., 2018). The modified Medical Research Council (mMRC) Dyspnea Scale was used to assess the amount of dyspnea during activities of daily living (ADL).

The presence of acute exacerbations in the preceding year were documented by consulting the medical files at Ziekenhuis Oost-Limburg.

3.4. Data analysis

Data analyses were performed using The IBM SPSS statistics 25 program (IBM Corp., 2017). Data are reported as means, standard deviations, confidence intervals, *p*-values, adjusted means, and odds ratios. The *p*-values below 0.05 were regarded as statistically significant. Differences between COPD participants with and without exacerbations in the previous year were studied while controlling for possible covariates. Controlling for variables improves the power of the analysis, which is necessary in this study because of the small sample size. Adjustments for confounders were based on 1) clinical relevance or 2) when the covariate had a proven influence on the dependent variable, based on evidence based literature, and 3) when the covariate was correlated with the dependent variable in the analysis. Baseline differences in characteristics were not considered as potential reasons for adjustments, because it does not improve the efficiency of the model and could lead to incorrect interpretations. In the article of de Boer et al., it is discussed that adjustments based on baseline imbalances could lead to irrelevant covariates and exclusion of important predictors (de Boer, Waterlander, Kuijper, Steenhuis, & Twisk, 2015).

Analyses of covariance (ANCOVA) were used to test for differences between groups for the continuous dependent variables, i.e. 4MGS, 6MWD, HGS, QMF, 5STS, weight change, FFM, and physical activity. The independent variable was defined as COPD exacerbation (yes/no). Confounders were continuous and/or categorical. Testing of assumptions was done before conducting the analyses.

An ordinal logistic regression model was used to test the effect of AECOPD in the previous year on fatigue levels (CIS Fatigue Scale). A binary logistic regression model was used to test for differences in functional status (SPPB). Both dependent variables can be measured as ordinal data. SPPB categorizes functional status in three categories, i.e. >9; 4-9; and <3. The CIS Fatigue Scale categorizes fatigue levels in three categories, i.e. normal, mild and severe fatigue (Goertz et al., 2018). For the SPPB data in this study, subjects were divided in only two categories (i.e. 4-9 and >9), which means the dependent variable could be considered binary. Confounders were continuous and/or categorical. Testing of assumptions was done before conducting the analyses.

Foundations of Clinical Research: Applications to Practice by L. G. Portney and M. P. Watkins was used to aid in the decision making process regarding statistical models, analysis and interpretation of results (Portney, L. G., Watkins, M. P. (2009). *Foundations of Clinical Research: Applications to Practice.* New Yersey: Pearson Education.).

4. Results

4.1. Subjects

A total of 24 subjects were included in the final cohort. Nine participants were defined as non-exacerbators and 15 participants had one or more exacerbations in the previous year. From these 15 participants, 4 participants were hospitalized.

Baseline characteristics of the participants are presented in table 1. Regarding the total cohort, the mean age was 66 ± 8 years, the mean weight 72.9 ± 17.5 kg, the mean BMI 25.65 kg/m² ± 4.04 and 54% was male.

One participant had tendovaginitis stenosans in both the left and right hand and was subsequently excluded from the analysis to test for differences in HGS. Two participants were excluded from the analysis of fatigue levels because the answers on the CIS Fatigue Scales contradicted each other and were therefore not valid. Five participants were excluded for the analysis of differences in weight change, because the available data was not recent (>2 years). The flowchart with the amount of participants that were excluded from various measurements is shown in figure 1.

4.2. Outcomes

COPD patients who experienced an exacerbation (AECOPD) in the preceding year had a mean score of 4.50 ± 0.85 seconds on the 4MGS while stable COPD patients had a mean score of 3.81 ± 1.07 seconds. AECOPD patients did not have a significant difference in 4MGS compared to stable COPD patients when corrected for age (p=0.088), however a trend towards significance can be seen. The individual 4MGS is shown in figure 2. The mean scores on the 5STS test were 12.40 ± 2.15 seconds and 10.94 ± 2.37 seconds for the AECOPD group and the stable group respectively. There was no significant difference between exacerbators and non-exacerbators for the 5STS test when corrected for age and BMI (p=0.079), but a trend towards significance can be noted. The individual 5STS performances are shown in figure 3. AECOPD patients had an average HGS of 33.9 ± 12.8 kg. Stable patients had an average HGS of 53 ± 12.4 kg. The comparison of the HGS between exacerbators and non-exacerbators showed no difference between the two groups when corrected for age, weight and gender (p=0.155). The individual HGS is shown in figure 4.

The mean QMF for the exacerbation group was 304.3 ± 88 N, the stable group had a mean value of 430.2 ± 154 N. There was no significant difference between the two groups when corrected for age, gender and weight (p=0.108). The individual QMF is shown in figure 5. Exacerbators covered on average 384.1 ± 129.9 m during the 6MWD, while non-exacerbators covered a mean distance of 466.7 ± 135.2 m. There was no statistically significant difference between the groups when corrected for age, BMI and gender (p=0.148). The individual 6MWD is shown in figure 6.

AECOPD patients gained on average 0.1 ± 6.7 kg in the preceding year, while stable patients lost 2.0 ± 5.7 kg. This weight change was not significantly different between the groups when adjusted for BMI and age (p=0.345). The FFM for the AECOPD and stable group were 44.9 ± 14.4 kg and 56.7 ± 12.4 kg respectively. The comparison of the FFM between the two groups showed no significant difference when corrected for age, gender and weight (p=0.544). The individual FFM is shown in figure 7. Patients who experienced an AECOPD took on average 3850 ± 1964 steps per day. The amount of steps per day for stable patients was 5157 ± 2125. The physical activity was not significantly different between the groups when adjusted for gender, age and BMI (p=0.084), but a trend towards less activity is shown. The individual physical activity levels are shown in figure 8**.** The risk of worse functional status for the AECOPD group was not significantly higher than the stable group when corrected for age and BMI (odds ratio (OR) 5.443, 95% CI: 0.181-163.857, p=0.329). The AECOPD group had no significant increased risk of severe fatigue levels compared to the stable group when corrected for age and BMI (odds ratio (OR) 2.034, 95% CI: 0.355-11.639, p=0.425). All adjusted means are presented in table 2.

5. Discussion

5.1. Interpretation of the results

The aim of this study was to investigate the association of AECOPD in the previous year with functional status parameters related to frailty. Based on the findings of this study, COPD exacerbations in the previous year are not significantly associated with worse functional status than stable COPD patients. The COPD exacerbation group had worse scores on all functional status tests, but after adjustment for confounders, these scores were not significantly different. However, a trend towards significantly worse scores can be noted for physical activity levels, quadriceps muscle force, four meter gait speed, and the five-repetition sit-to-stand test. Because of the small sample size, these results need to be interpreted with caution.

5.2. Comparison with other literature

COPD patients with AECOPD in the previous year, walked on average 85.54m less than stable COPD patients on the 6MWD when adjusted for confounders. This difference in exercise capacity, although not statistically significant, could be explained by systemic inflammation over time, especially for frequent exacerbators, worse respiratory mechanics, reduced muscle force, fatigue, fear and other factors. In this study, AECOPD patients had lower QMF, which could be one of the factors associated with a decline in 6MWD.

The effect of AECOPD on exercise capacity during the hospitalization period is clear. Both Alahmari et al. and Cote et al. reported a significant decline in 6MWD during the hospitalization period compared with pre-AECOPD status (Alahmari et al., 2014; Cote, Dordelly, & Celli, 2007). The influence of AECOPD on exercise capacity after the hospitalization period is less clear. A significant increase in 6MWD one month after the hospitalization period can be seen in the studies of Pitta et al. and Borges et al. and a significant increase after 6 weeks was reported in the study of Tsai et al (Borges & Carvalho, 2012; Pitta et al., 2006; Tsai, Alison, McKenzie, & McKeough, 2016). A study of Cote et al. reported a significant decline of 37m in 6MWD, 6 months post-AECOPD compared to pre-AECOPD status, and a significant decline of 49m after one year (Cote et al., 2007). The study of Ramon et al. reported a decline of 32.6m per year for hospitalized COPD patients (Ramon et al., 2014).

In the study of Cote et al., a significant decline of 72m was also reported 2 years after the AECOPD (Cote et al., 2007). The article of Dreyse et al. contradicts these findings and reports no significant differences 2 years after the index event (Dreyse et al., 2015).
There are some differences between these studies, but a trend towards a linear decrease in exercise capacity can be seen over time.

There was a difference of 1.57 seconds between the groups on the 5STS after the correction. AECOPD patients needed more time to perform the five consecutive maneuvers. A lack of muscle strength could be one of the determining factors for this test. Comparing the HGS and QMF between the groups after correction showed differences of 6.91 kg and 76.55 N respectively. These differences were in favor of the non-exacerbators.
Martinez et al. reported that a decrease in HGS is associated with an increase in exacerbation risk (Martinez et al., 2017).
A significant decline in quadriceps strength can be seen the first week after the index exacerbation (Alahmari et al., 2016; Alahmari et al., 2014; Burtin et al., 2011; Pitta et al., 2006; Spruit et al., 2003). In the study of Spruit et al., there was a 1% reduction of peak quadriceps torque per day during an inpatient exacerbation, but a significant increase of 6% 90 days after discharge compared to the end of the hospitalization period (Spruit et al., 2003). In the study of Borges et al., there was also no change in quadriceps strength one month after discharge, compared to the hospitalization period (Borges & Carvalho, 2012). Many factors can impair QMF. During the hospitalization period, AECOPD patients are in the state of being bedridden, with a decrease in nutritional intake and increased resting energy expenditure (Troosters, Probst, et al., 2010). A decline in strength could also be explained by pathways of systemic inflammation, altered medication, energy depletion, and a dysregulation of hormone levels (Burtin et al., 2011; Crul et al., 2010; Kamischke et al., 1998; Karadag et al., 2009; Sinden & Stockley, 2010; Spruit et al., 2003; Van Vliet et al., 2005; Vermeeren et al., 1997). High doses of corticosteroids could lead to decreased anabolic hormone levels (Burtin et al., 2011).
Based on these studies, QMF is significantly impaired the first week after the onset of AECOPD symptoms, with a normalization after approximately one month. It is not clear what the medium-term and long-term effects of an AECOPD on muscle strength actually are.
In the current study, although not statistically significant, QMF was more impaired in the AECOPD group. This could be due to a vicious cycle of readmissions and the impact on systemic inflammation, energy levels, altered medication and other factors.

Vilaro et al. stated that readmissions lead to a decrease in HGS and global muscle function (Abdulai et al., 2018; Vilaro et al., 2010). Conversely, a decreased muscle function leads to elevated risk levels for readmission (Abdulai et al., 2018; Greening et al., 2015; Vilaro et al., 2010).

Another hypothesis could be that COPD patients only actively rehabilitate during the first weeks after the onset of exacerbation symptoms until normal strength is attained. There could also be differences in pulmonary rehabilitation, with an effect on functional status parameters. The differences between both groups in the current study could also be explained by the fact that the sample size was small, which means the results need to be interpreted with caution.

Patients in the AECOPD group were less active than stable patients. A difference of 1395 steps/day was observed in favor of the stable group after correction. A reduction in daily physical activity could have a negative impact on muscle strength and other functional measures.

Physical activity declines during the first weeks after the onset of exacerbation symptoms in inpatient and outpatient exacerbators, with a linear increase the next month, but still under mean values of stable COPD patients (Alahmari et al., 2016; Alahmari et al., 2014; Ehsan et al., 2013; Pitta et al., 2006). Borges et al. report similar findings, with an average of 7.2 minutes walking time per day during the admission period and a significantly increased walking time after one month (Borges & Carvalho, 2012). The same trend can be seen in the study of Tsai et al., where steps/day increased one week and six weeks after discharge, compared to total steps/day during the admission period (Tsai et al., 2016).

Physically less active COPD patients have a higher chance for being hospitalized and readmitted due to exacerbations (Chawla, Bulathsinghala, Tejada, Wakefield, & ZuWallack, 2014; Esteban et al., 2014; Moy, Teylan, Weston, Gagnon, & Garshick, 2013). These findings are in line with the study of Garcia-Aymerich et al. who observed that the risks of being readmitted were lowered by 50% for patients who were physically active for 60 min/day (Garcia-Aymerich et al., 2003).

These findings indicate decreased physical activity levels during the first weeks and one month after the index AECOPD. An explanation for low physical activity levels during the first weeks is the influence of a hospital admission. The patients then need to perform activities of daily living again after hospital discharge, which leads to increased activity levels. Impaired respiratory mechanics, muscle wasting, fatigue, altered medication, increased systemic inflammation and other impaired functional parameters could also have a negative effect on physical activity levels the first weeks and months after the index exacerbation, which could remain decreased long-term. This could explain the differences in the current study.

AECOPD patients were, after correction for confounders, on average 0.71 seconds slower than stable patients when performing the 4MGS. Calculating the actual gait speed shows that exacerbators had an average speed of 0.89 m/sec while non-exacerbators traveled at a speed of 1.05 m/sec. A study by Castell et al. showed that a gait speed of >0.9 m/s could rule out frailty and that a speed of <0.8 m/s would double the chances of being frail (Castell et al., 2013). According to Kon et al., decreased 4MGS results in increased admission risk. In that study, COPD patients had a mean 4MGS of 0.61 m/s at the end of the admission period, which is below the threshold of 0.8 m/s (Kon et al., 2015).

These findings suggest that admitted COPD patients have decreased gait speed which could indicate frailty. In the current study, AECOPD patients had higher gait speed than the COPD patients in the study of Kon et al., which could be due to the acute hospitalization, differences in baseline characteristics or exacerbation severity.

The difference in weight change was 3,4 kg across the groups after the correction. The difference was in favor of the AECOPD group, which means that the exacerbators lost less body weight. For the FFM there was a difference of 0.78 kg in the corrected means between the groups, with the exacerbators having the lower value.

COPD patients have a high incidence of malnutrition, defined as low FFM values (Luo et al., 2016). Frequent exacerbations lead to a decline in FFM (Dolan & Varkey, 2005; Hallin, Koivisto-Hursti, Lindberg, & Janson, 2006; Luo et al., 2016).

These findings are not consistent with the current study, which could be due to a small sample size or a limited number of frequent exacerbators in the AECOPD group. In the study of Pitta et al., FFM did not change during the hospitalization period and one month after discharge (Pitta et al., 2006). These results are similar with the results of our study, but should be interpreted with caution because of differences in follow-up periods.

According to the study of Hallin et al., where weight change was measured in COPD patients during a follow-up of 12 months, weight loss and being underweight were correlated with increased exacerbation risk. In the same study, all COPD patients had energy deficiencies one year after the admission period, because of a disbalance in energy intake versus demand (Hallin et al., 2006). These findings are supported by the study of Pouw et al., where weight loss was correlated with readmission risk (Pouw et al., 2000). The results in our study contradict these findings, which could be explained by the small sample size or the low number of previously admitted COPD patients.

A hypothesis could be that COPD patients admitted for AECOPD have more weight loss than outpatient exacerbators due to different factors, i.e. the state of being bedridden, the severity of exacerbations and systemic inflammation. Another factor could be the increased resting energy expenditure (REE) during the hospitalization period (Vermeeren et al., 1997). The studies of Pitta et al and Vermeeren et al. contradict this hypothesis, because of a higher dietary intake during the admission period compared to the pre-AECOPD status (Pitta et al., 2006; Vermeeren et al., 1997). This would counterforce the elevated REE and result in no weight or BMI difference.

There was no significant difference in fatigue levels between both groups. However the risk for severe fatigue levels is 2.034 higher for the AECOPD group compared to the stable group.
In the article of Baghai-Ravary et al., AECOPD resulted in significantly increased fatigue levels during the hospitalization period. The fatigue levels normalized 6 weeks after the index exacerbation (Baghai-Ravary et al., 2009). This is in line with the current study because patients were included in the exacerbation group if they had experienced an exacerbation in the previous year, which means fatigue levels could have already been normalized after the index exacerbation.
In the article of Baghai-Ravary et al., it is also mentioned that greater fatigue levels lead to an increase in exacerbation frequency (Baghai-Ravary et al., 2009). This could lead to a vicious cycle of readmissions and reduced fatigue levels, which could lead to increased frailty.

The SPPB measures functional status and consists of three test items. A balance test, the 5STS and the 4MGS. In the current study, there were no significant differences between both groups for SPPB scores, however the risk for worse functional status is 5.433 higher for the AECOPD group compared to the stable group. These findings need to be interpreted with caution because of the small sample size.
According to Oliveira et al., stable and hospitalized COPD patients have more balance impairments than healthy controls. The AECOPD group performed worse on posturography tests than the stable COPD group and had more falls in the same year (Oliveira et al., 2017). Differences in 5STS and 4MGS are depicted above.
The findings suggest that there could be a difference in SPPB scores or functional status between stable COPD and AECOPD patients. The difference could be most significant at the time of hospitalization. Muscle strength and gait speed, as depicted earlier, are significantly decreased during the admission period, which could result in decreased functional status or SPPB scores.

To our knowledge, no study exists, which compares SPPB scores between hospitalized and stable COPD patients.

COPD patients are more frail than their healthy counterparts (Valenza et al., 2016). The findings in the current study and the comparisons with other literature suggest that AECOPD could lead to increased frailty because of worse scores on functional parameters associated with frailty. AECOPD could lead to a vicious circle of impairment, inactivity, impaired respiratory mechanics, admissions and readmissions, which could result in increased frailty (Lahousse et al., 2016; Valenza et al., 2016).

5.3. Strengths and limitations

One of the strengths of the current study is the correction for confounding variables during the statistical analysis. Another strength is the fact that various valid and reliable functional tests were used to examine the functional status. The tests that were used can also be used to examine the concept of frailty with the modified frailty index by Fried et al. Finally an extensive comparison was made between the findings of this study and already existing literature.

There are some limitations. This study consisted of a small sample size, which reduces the power of the study and therefore makes generalization of the findings more challenging. The generalization for women who experience an AECOPD is difficult because of the fact that 89% of the participants in the exacerbator group were male. The limited amount of COPD patients that were previously admitted for an AECOPD also had an unfavorable impact on the ability to generalize the results. The study has a cross sectional design which makes it harder to explore causal relationships between AECOPD and functional status parameters. The medical files were used to assess exacerbations in the previous year. This makes it harder to check if the GOLD criteria for an AECOPD were met, which is a limitation. The AECOPD were observed in a retrospective manner and it is therefore only possible to observe long term effects of the event. Another limitation is that there were missing data from various tests which makes it more challenging to generalize the findings and which made it difficult to assess frailty by using the modified frailty index by Fried et al. Lastly, the measurements were carried out by five different researchers, which might have an influence on the reliability of the results, especially for those tests where the skill of the researcher plays an important role.

For future research it would be interesting to have a larger sample size and a longitudinal design to examine the effects of an AECOPD on functional status parameters. A longitudinal design would make it possible to have both pre- and post-exacerbation measurements of the functional status, which could be of great value to analyze short- and long term effects.

6. Conclusion

COPD patients who experienced AECOPD in the preceding year, although not significantly different, performed worse on all functional parameters associated with frailty, except for FFM and weight loss. These conclusions are based on the results after correction for confounders. The findings of the current study showed similarities with other literature, which means the results could be representative for the target population. Future research with larger sample sizes and with a comparison of functional status between pre- and post-AECOPD measurements are needed.

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8. Appendices

8.1. Appendix A

Figure 1. Flowchart participants and exclusion from data analysis.

Table 1: Baseline Characteristics

Table 2: Means after correction for covariates

Figure 2. Individual 4MGS (time) for exacerbators and non-exacerbators.

Figure 3. Individual 5STS performance (time) for exacerbators and non-exacerbators.

Figure 4. Individual HGS (kg) for exacerbators and non-exacerbators.

Figure 5. Individual QMF (N) for exacerbators and non-exacerbators.

Figure 6. Individual 6MWD (m) for exacerbators and non-exacerbators.

Figure 7. Individual FFM (kg) for exacerbators and non-exacerbators.

Figure 8. Individual physical activity levels (steps/day) for exacerbators and non-exacerbators.

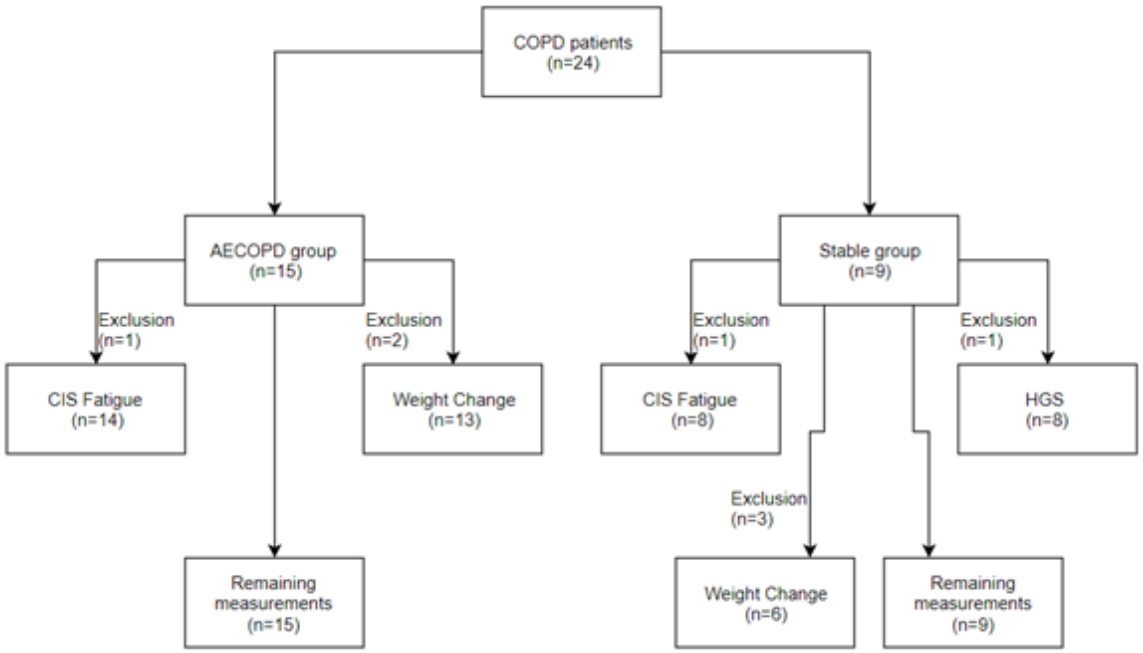

Figure 1. Flowchart participants and exclusion from data analysis.

COPD=chronic obstructive pulmonary disease, AECOPD=acute exacerbations of COPD, CIS=checklist individual strength, HGS=hand grip strength.

Table 1
Baseline Characteristics

Baseline Characteristics	Exacerbators (n=15)	Non-exacerbators (n=9)
Age (yr), *M ± SD*	65.40 ± 5.26	66.56 ± 12.17
Height (cm), *M ± SD*	164.50 ± 10.71	174 ± 10.42 *
Weight (kg), *M ± SD*	70.14 ±17.10	77.22 ± 18.12
BMI (kg/m²), *M ± SD*	25.85 ± 3.95	25.30 ± 4.40
Male gender, n (%)	5 (33.3)	8 (88.9) *
FEV1 (L), *M ± SD*	1.34 ± 0.60	1.63 ± 0.60
FEV1 (%), *M ± SD*	54.80 ± 20.20	53.78 ± 15.43
FEV1/FVC (%), *M ± SD*	53.27 ± 9.76	50.54 ± 8.86
mMRC, n (%)		
0	4 (28.6)	1 (12.5)
1	1 (7.1)	3 (37.5)
2	4 (28.6)	2 (25)
3	4 (28.6)	1 (12.5)
4	1 (7.1)	1 (12.5)

Note. Abbreviations: *M*=mean, *SD*=standard deviation, yr=years, cm=centimeters, kg=kilograms, kg/m²= kilograms per meter square, n=number, FEV1=forced expiratory volume 1st second, FEV1/FVC=Tiffeneau-index, mMRC=modified Medical Research Council Dyspnea Scale, L=litres.

* *p value* < 0.05

Table 2
Means After Correction For Covariates

Outcome	Exacerbators (n=15) *M*	Non-exacerbators (n=9) *M*
4MGS (sec)	*4.51*	*3.80*
5STS (sec)	*12.44*	*10.87*
HGS (kg)	*38.13*	*45.04*
QMF (N)	*323.99*	*400.54*
6MWD (m)	*383*	*468.54*
Weight change (kg)	*0.58*	*-2.83*
FFM (kg)	*49.55*	*50.33*
Physical activity (steps/day)	*3812.75*	*5208.47*

Note. Abbreviations: *M*=mean, n=number, 4MGS=4 meter gait speed, 5STS=5-repetition sit-to-stand test, HGS=handgrip strength, QMF=quadriceps muscle force, 6MWD=6 minute walking distance, FFM=fat-free mass, sec=seconds, kg=kilograms, N=Newton, m=metres.

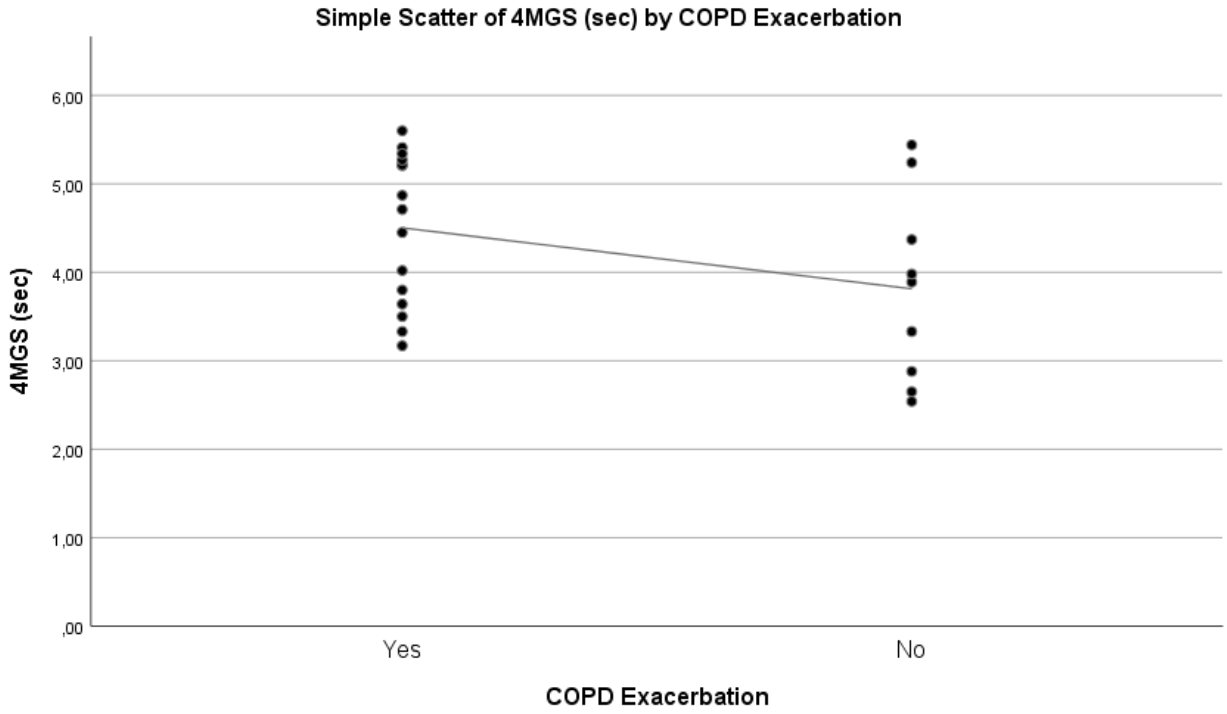

Figure 2. Individual 4MGS (time) for exacerbators and non-exacerbators.

——: interpolation line between means of both groups. 4MGS=four meter gait speed, sec=seconds, COPD=chronic obstructive pulmonary disease.

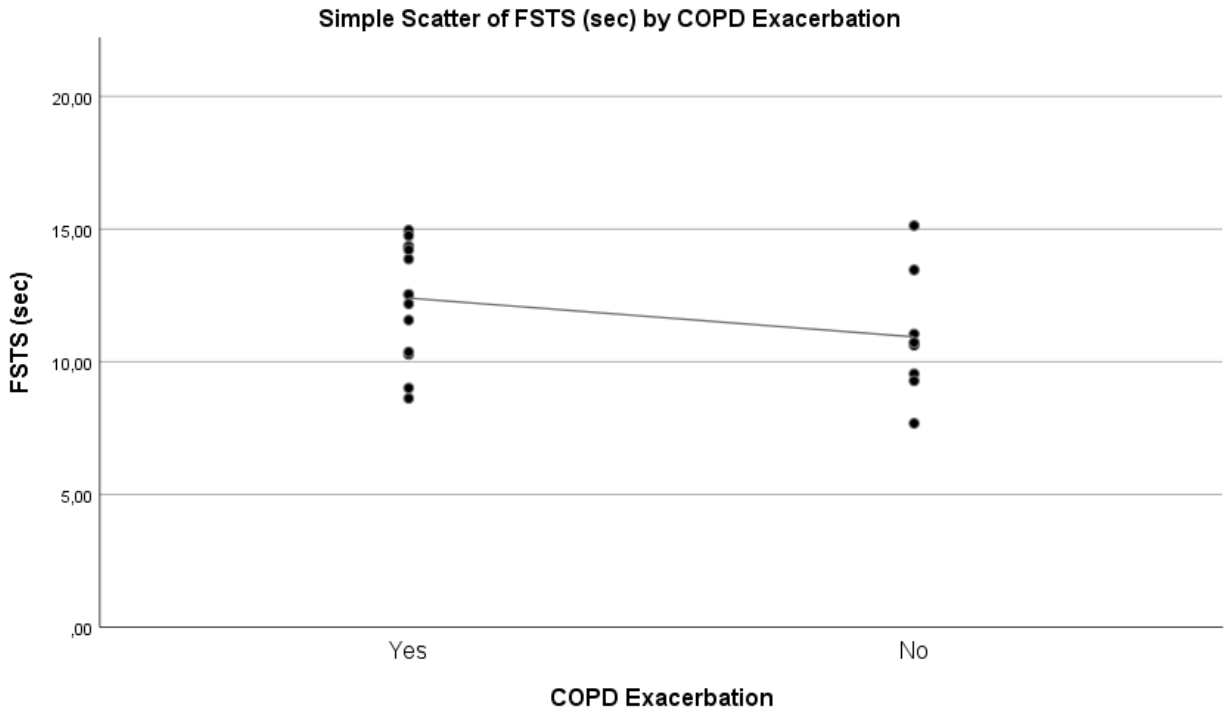

Figure 3. Individual 5STS performance (time) for exacerbators and non-exacerbators.

——: interpolation line between means of both groups. FSTS=five-repetition sit-to-stand test, sec=seconds, COPD=chronic obstructive pulmonary disease.

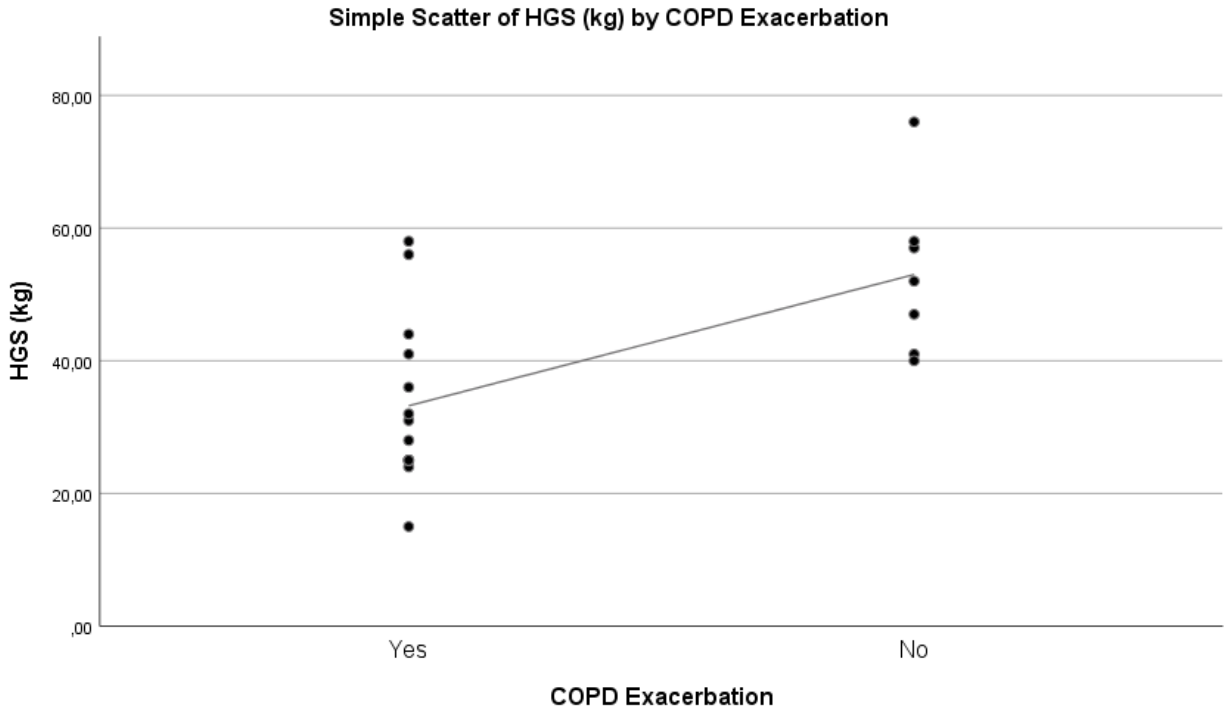

Figure 4. Individual HGS (kg) for exacerbators and non-exacerbators.

——: interpolation line between means of both groups. HGS=handgrip strength, kg=kilograms, COPD=chronic obstructive pulmonary disease.

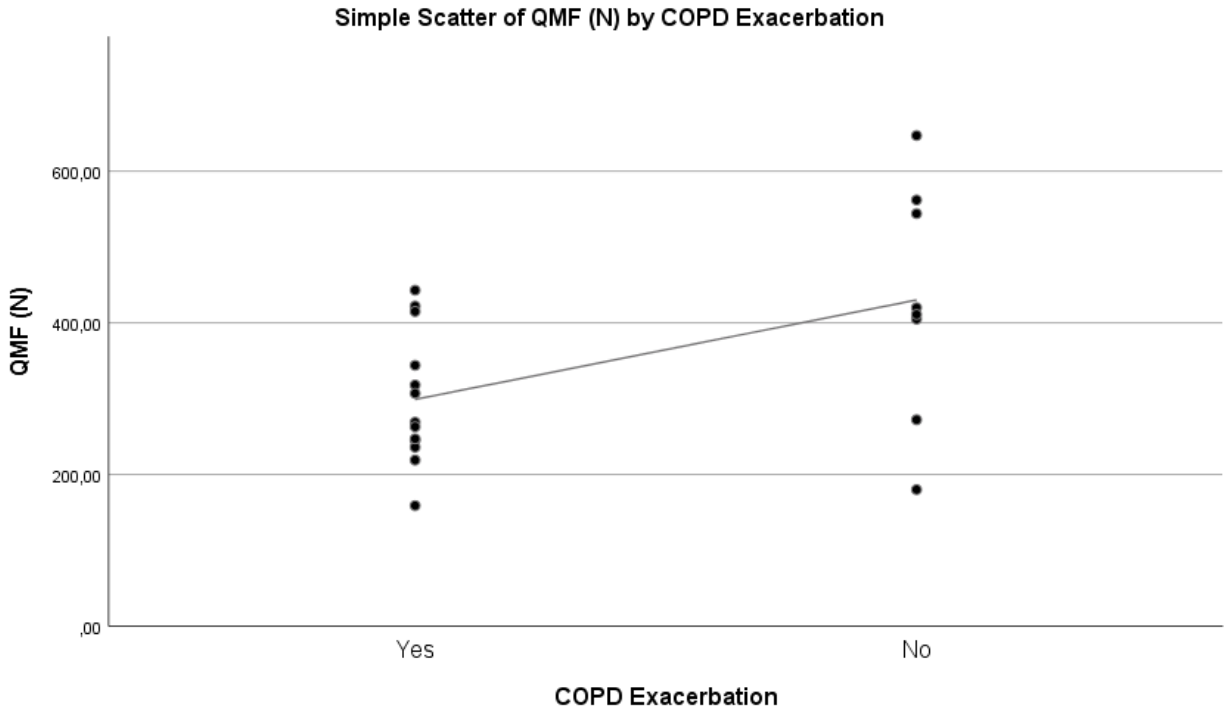

Figure 5. Individual QMF (N) for exacerbators and non-exacerbators.

——: interpolation line between means of both groups. QMF=Quadriceps muscle force, N=Newton, COPD=chronic obstructive pulmonary disease.

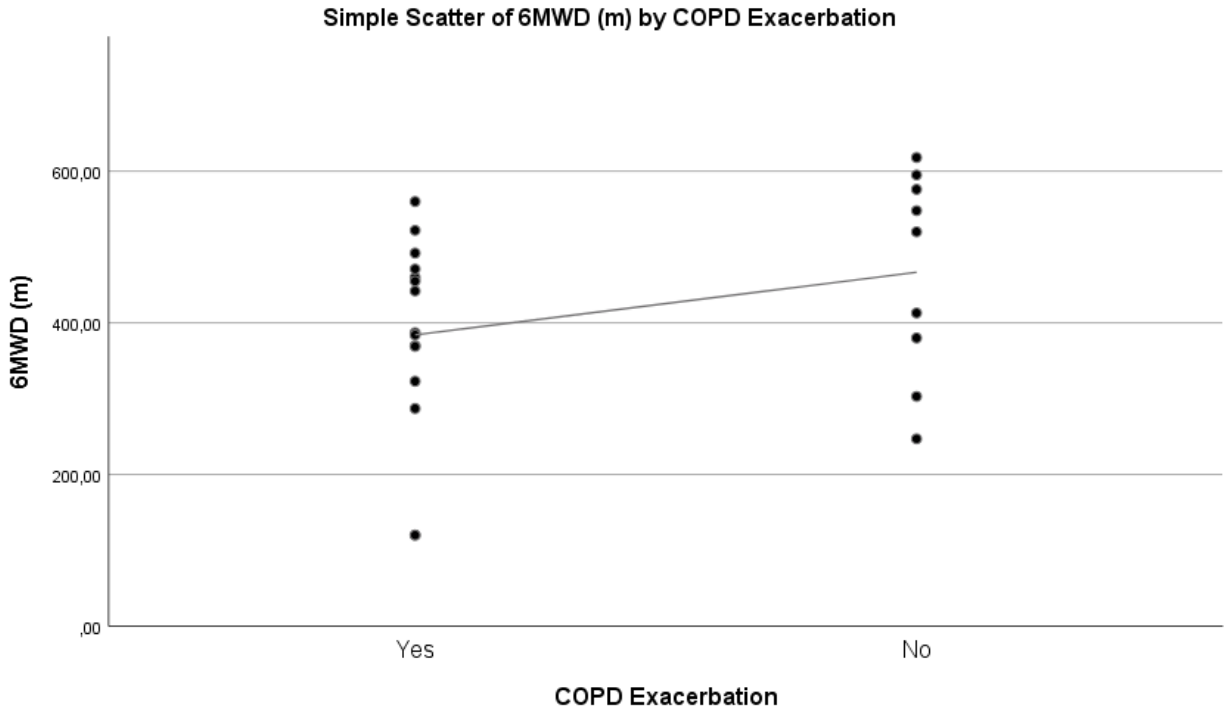

Figure 6. Individual 6MWD (m) for exacerbators and non-exacerbators.

——: interpolation line between means of both groups . 6MWD=six minute walking distance, m=metres, COPD= chronic obstructive pulmonary disease.

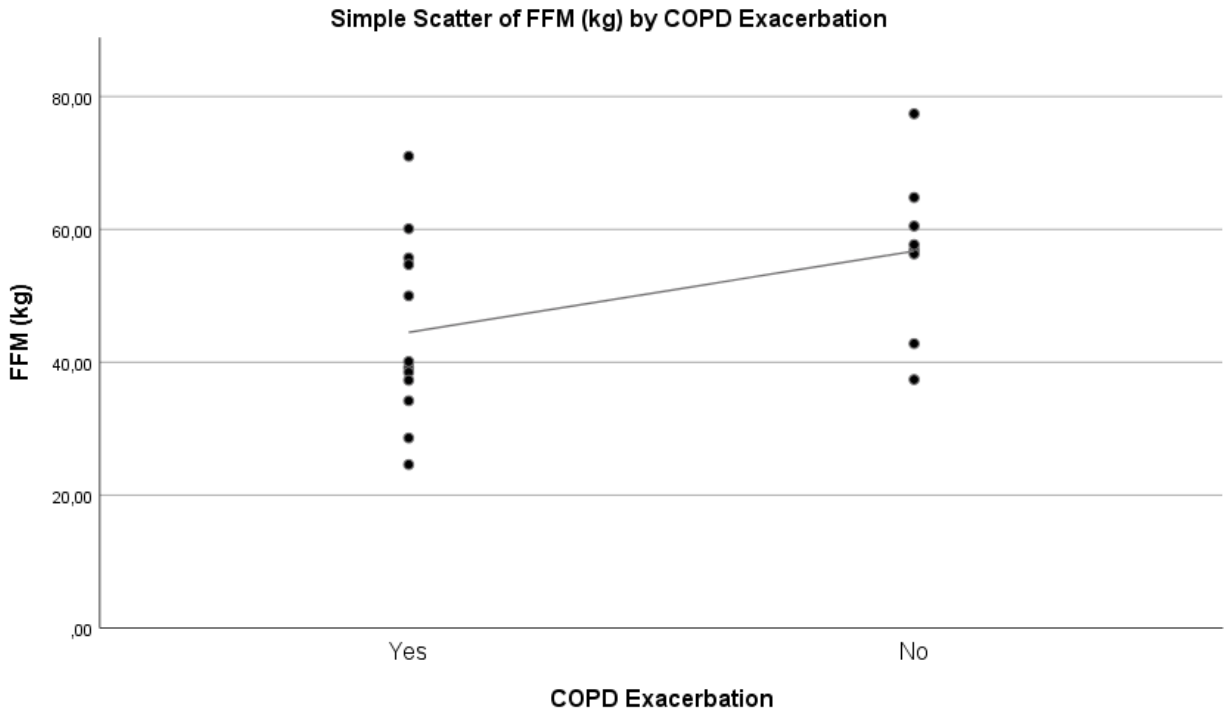

Figure 7. Individual FFM (kg) for exacerbators and non-exacerbators.

——: interpolation line between means of both groups. FFM=fat-free mass, kg=kilograms, COPD=chronic obstructive pulmonary disease.

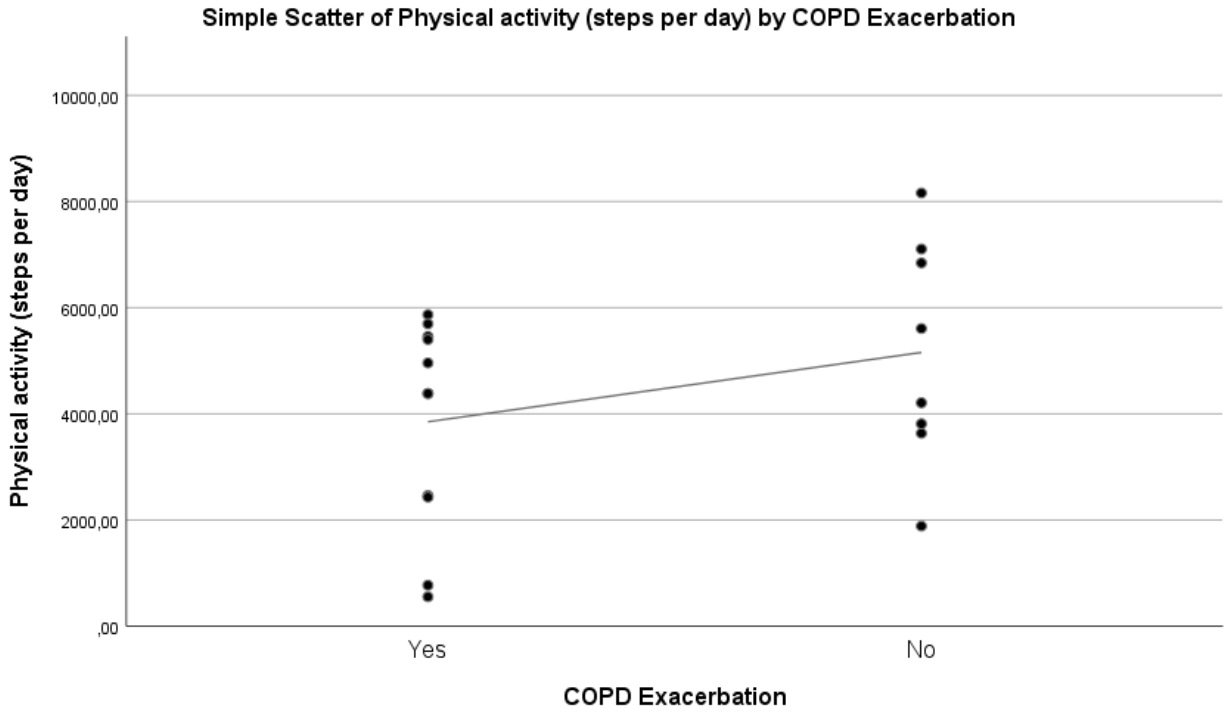

Figure 8. Individual physical activity levels (steps/day) for exacerbators and non-exacerbators.

——: interpolation line between means of both groups. COPD=chronic obstructive pulmonary disease.

8.2. Appendix B

In-depth statistical analysis

The following key assumptions were checked for the analyses of covariance: a continuous dependent variable and a categorical independent variable; independence of observations; normally distributed data (Shapiro-Wilk test); homogeneity of variances (Levene's test); no multicollinearity between the confounders (Pearson's r); a linear relationship of each covariate with the dependent variable for every level of the independent variable (Scatter plot); and homogeneity of regression slopes (non-significant interaction effects).

The following key assumptions were checked for the ordinal logistic regression models: an ordinal dependent variable and categorical or continuous independent variables; no multicollinearity between independent variables (Pearson's r); and proportional odds of each independent variable (Test of Parallel Lines).

Assumptions for the binary logistic regression model: a dichotomous dependent variable and categorical or continuous independent variables; independence of observations; and a linear correlation between the continuous independent variables and the log odds (Box-Tidwell Test).

For the analysis to test for differences between groups for the 4MGS, age was included as a potential confounder based on clinical relevance and proven influence (Butler, Menant, Tiedemann, & Lord, 2009). BMI could be included based on clinical relevance, but was excluded because of minimal correlation with the dependent variable (r= 0.005). Gender has no proven influence on normal gait speed, so it was excluded from the analysis (Ko, Tolea, Hausdorff, & Ferrucci, 2011). All assumptions of the model were met.

To test for differences in 5STS, age and BMI were included as potential confounders, based on the articles of Butler a. et al. and Bohannon et al. respectively. Gender could be included based on the article of Butler et al., where some gender differences were reported, but was excluded based on the article of Bohannon et al, a bad correlation with the dependent variable and violation of the assumption of linearity with the dependent variable for each level of the independent variable and homogeneity of regression slopes (Bohannon, Shove, Barreca, Masters, & Sigouin, 2007; Butler et al., 2009). All the assumptions of the final model were met.

Differences in hand grip strength and quadriceps muscle force were tested while controlling for age, gender and weight. These confounders were included based on clinical relevance and correlations with the dependent variable. All assumptions of both analyses were met, except for violation of collinearity of the covariates, linearity of gender with the dependent variable for each level of the independent variable, and homogeneity of regression slopes.

Gender and age were significantly correlated with each other but were kept in both models because of important predictors for strength. The assumptions of linearity and homogeneity of regression slopes were violated because no fit line of the plot and no interaction effect could be tested. The explanation for this is that there were only men in the non-exacerbation group for both analyses. Because of the importance of gender as a predictor for strength, the confounder was still included in both models. The results of these analyses need to be interpreted with caution.

Differences in 6MWD were analyzed while adjusting for age, gender and BMI. Confounders were included based on the articles of Troosters et al. and Shrestha et al. (Shrestha & Srivastava, 2015; Troosters, Gosselink, & Decramer, 1999). All assumptions for conducting an ANCOVA were met.

Differences in weight change were analyzed while controlling for age and BMI. BMI was included based on clinical relevance and age based on 'factors that influence body weight'. All assumptions of the model were met.

Age, gender and weight were included as covariates to test for differences in FFM. These variables were included based on clinical grounds and strong correlations with the dependent variable. Linearity of age with FFM for the exacerbation group was violated because of minimal correlation (r= 0.001). Linearity of gender with FFM for the exacerbator group was violated because there were only men in the exacerbation group and no interaction effect could be tested. Two assumptions were violated but the confounders were still included in the analysis. The model still adjusts for both confounders even though some assumptions were violated. Interpretation with caution is necessary.

Differences in physical activity levels were tested while controlling for age and BMI. Both confounders were included based on clinical grounds. Gender was excluded because of no proven influence on physical activity levels (Pollard & Wagnild, 2017). All assumptions except for normally distributed data were met (p=0.031). The assumption of normality was met when significant outliers were removed from the model.

Age and BMI were included in the analysis of differences in functional status (SPPB). Age was excluded from the model based on the article of Gomez et al. (Gomez, Curcio, Alvarado, Zunzunegui, & Guralnik, 2013). The assumption of proportional odds was violated. No parallel lines could be tested because of a zero chi square value. Binary logistic regression was used as a solution. The SPPB scale has three categories, but in this study data, subjects were divided in only two categories (i.e. 4-9 and >9), which means the dependent variable is binary. All the assumptions of the final model were met.

To test for differences in fatigue levels (CIS Fatigue Scale), both age and BMI were included based on clinical relevance. Gender was excluded from the analysis (Theander & Unosson, 2011). All the assumptions of ordinal logistic regression were met.

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