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

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

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ABSTRACT

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

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

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

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

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

BACKGROUND

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

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

METHODS

Study design

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

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

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

Study population

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

Data collection

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

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

Statistical analysis

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

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

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

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

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

RESULTS

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

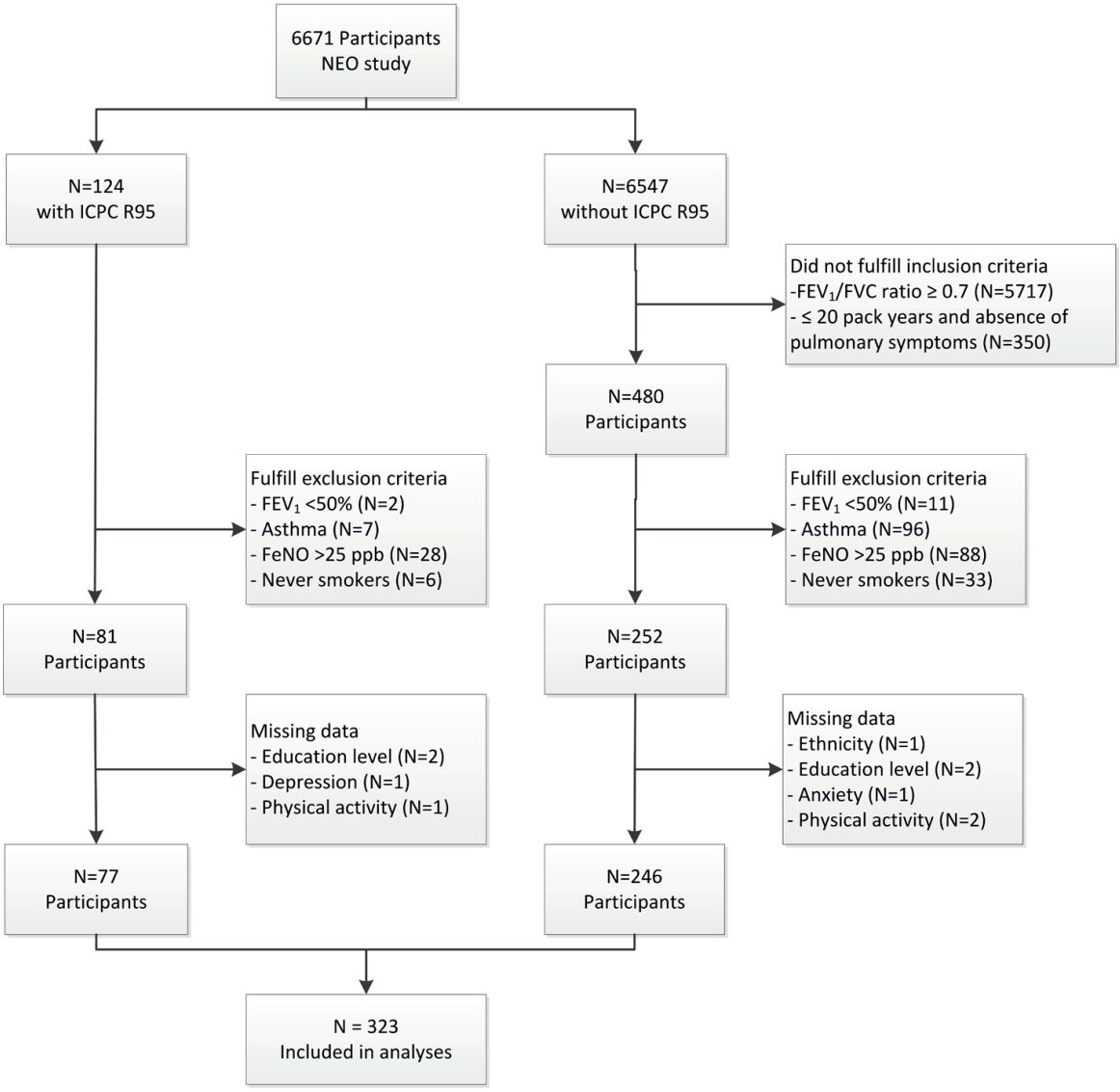

Figure 1 Flow chart of study design

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

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

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

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

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

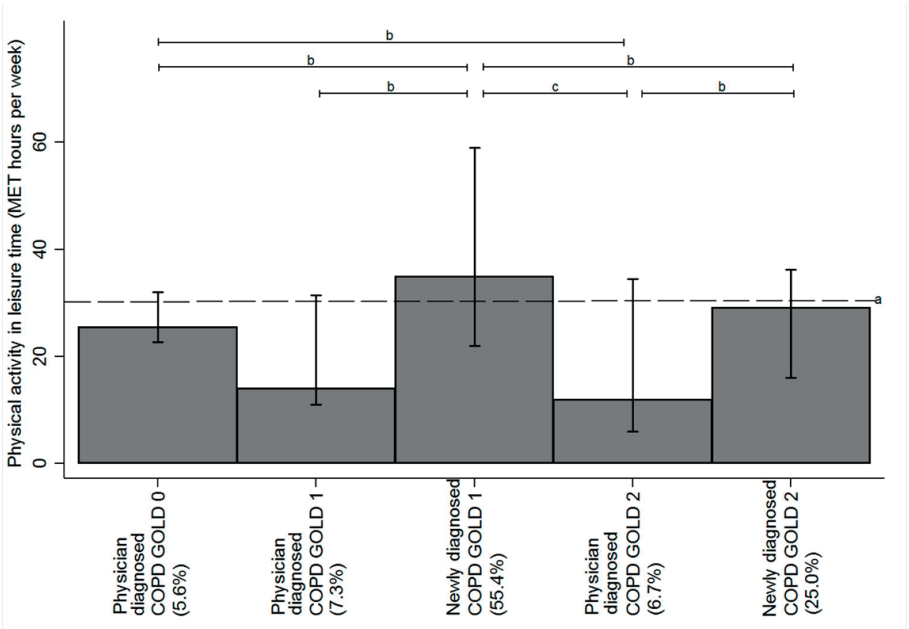

Figure 2 Physical activity in physician diagnosed and newly diagnosed COPD GOLD 0, 1 and 2
COPD: Chronic obstructive pulmonary disease; GOLD: global initiative for chronic obstructive lung disease; MET: metabolic equivalent task; NEO: Netherlands Epidemiology of Obesity
Bar plots represent the medians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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

Strengths and limitations

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

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

CONCLUSIONS

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

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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

CONSENT FOR PUBLICATION

Not applicable

DATA AVAILABILITY STATEMENTS

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

COMPETING INTERESTS

All authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

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

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LIST OF ABBREVIATIONS

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

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SUPPLEMENTARY MATERIALS

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

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

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