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The COgnitive-Pulmonary Disease (COgnitive-PD) study: protocol of a longitudinal observational comparative study on neuropsychological functioning of patients with COPD

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ABSTRACT

Introduction: Intact cognitive functioning is necessary for patients with chronic obstructive pulmonary disease (COPD) to understand the value of healthy lifestyle guidelines, to make informed decisions and subsequently act on it. Nevertheless, brain abnormalities and cognitive impairment have been found in patients with COPD. To date, it remains unknown which cognitive domains are affected and what the possible consequences are of cognitive impairment. Therefore, objectives of the study described are to determine neuropsychological functioning in patients with COPD, and its influence on health status, daily functioning and pulmonary rehabilitation outcome. Furthermore, structural and functional brain abnormalities and the relationship with cognitive and daily functioning will be explored.

Methods and analysis: A longitudinal observational comparative study will be performed in 183 patients with COPD referred for pulmonary rehabilitation and in 90 healthy control participants. Demographic and clinical characteristics, activities of daily living and knowledge about COPD will be assessed. Baseline cognitive functioning will be compared between patients and controls using a detailed neuropsychological testing battery. An MRI substudy will be performed to compare brain abnormalities between 35 patients with COPD with cognitive impairment and 35 patients with COPD without cognitive impairment. Patients will be recruited between November 2013 and November 2015.

Ethics and dissemination: The study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035) and is registered in the Dutch trial register. All participants will provide written informed consent and can withdraw from the study at any point in time. Assessment and home visit data material will be managed anonymously. The results obtained can be used to optimise patient-oriented treatment for cognitively impaired patients with COPD. The findings will be disseminated in international peer-reviewed journals and through research conferences.

Strengths and limitations of this study

- The study uses a comprehensive neuropsychological testing battery and novel imaging techniques to investigate cognitive functioning in specific cognitive domains and functional and structural brain abnormalities.
- Recruitment in a pulmonary rehabilitation centre allows exploration of the effects of cognitive impairment on pulmonary rehabilitation outcomes and daily functioning in patients with COPD.
- This approach could potentially limit generalisation of the results due to recruitment of patients who experience limitations in daily life activities.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease of the lungs, that is usually progressive.[1] It is a major course of morbidity and mortality worldwide.[2] Patients with COPD often suffer from extrapulmonary features, such as cardiovascular disease, exercise intolerance, osteoporosis and psychological symptoms.[1 3–5] Patients with COPD may suffer from cognitive impairment.[6] The incidence of cognitive impairment in patients with COPD varies in different studies from 12% to 88%.[7] It may lead to increased dyspnoea and fatigue,[8] incorrect use of inhaler devices and low compliance with medical treatment.[9] This might increase the exacerbation risk and could result in worse health outcomes.[10] Indeed, cognitive impairment has been found to predict mortality in hypoxaemic patients with COPD.[11]

A recent review article indicates a specific pattern of cognitive impairment in patients with COPD.[12] This suggests that COPD is

associated with specific abnormalities in brain structure. However, cognitive functioning has mostly been studied with broad-scale measurements, which do not separate specific cognitive functions, such as psychomotor speed, memory, cognitive flexibility and planning.[13] Therefore, no clear statement can be made about the incidence and clinical implications of cognitive impairment in specific cognitive domains in patients with COPD. Insight in cognitive functioning is of great importance in order to optimise self-management skills of patients with COPD. Indeed, cognitive deficits may lead to difficulties in managing their disease and negatively affect their treatment and, in particular, the efficacy of a pulmonary rehabilitation programme.[14] Therefore, the aim of this study is to compare cognitive functioning in patients with COPD referred for pulmonary rehabilitation and participants without COPD. More specific objectives of the present study are to:

1. Examine whether and to what extent cognitive functioning is impaired in patients with COPD referred for pulmonary rehabilitation, compared with a control group matched on smoking status, age and educational level without COPD in the following domains: psychomotor speed, memory, cognitive flexibility and planning;
2. Investigate clinical and demographic characteristics of patients with COPD with cognitive impairment;
3. Explore whether and to what extent cognitive functioning of patients with COPD referred for pulmonary rehabilitation is related to problems in daily functioning;
4. Examine whether and to what extent cognitive functioning affects outcomes of pulmonary rehabilitation (general psychological functioning, knowledge about COPD, need for information, daily functioning and functional exercise capacity);
5. Determine the presence of functional and structural brain abnormalities in patients with COPD with and without cognitive dysfunction.

We hypothesise that patients with COPD with more severe airflow limitation have worse cognitive functioning on all of the aforementioned domains, compared with patients with less severe disease. Moreover, patients with COPD have worse cognitive functioning compared with healthy controls. Furthermore, patients with COPD with cognitive impairments will potentially have worse clinical characteristics, experience more often limitations in daily functioning and have worse outcomes of pulmonary rehabilitation compared with patients with COPD without cognitive impairment. Finally, patients with COPD with brain abnormalities are suspected to have more often cognitive impairments and to experience more often limitations in daily functioning.

METHODS AND ANALYSIS

Study design

A longitudinal observational comparative study will be performed. Patients who enter pulmonary rehabilitation at CIRO+ will be recruited between November 2013 and November 2015. They are referred to CIRO+ for interdisciplinary assessment when they are symptomatic or they report having decreased daily life-activity at outpatient consultation with their chest physician, even if receiving optimum drug treatment. During the 3-day assessment at CIRO+, centre of expertise for chronic organ failure,[15] patients will be invited to participate in the study. The 3-day assessment includes as part of the clinical routine the evaluation of physical functioning, psychosocial functioning, coexisting morbidities, exercise capacity, daily functioning and health status, as published before.[5 16] Before the start of the pulmonary rehabilitation programme, the patient will be visited at home for neuropsychological examination. After completion of the pulmonary rehabilitation programme, all patients will undergo an outcome assessment. Baseline test will be repeated and the results of initial and outcome assessments will be available for the study in the electronic patient's record.

As part of an MRI substudy, a subgroup of the patients with COPD will undergo MRI of the brain to determine the presence of brain abnormalities in patients with COPD with and without cognitive impairment. MRI will be performed after the 3-day assessment and before the start of the pulmonary rehabilitation programme (see figure 1).

Study population

In total, the study will include 183 patients with clinically stable COPD, based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document,[1] referred for pulmonary rehabilitation. Participants with clinically unstable COPD in the past 4 weeks, participants with a diagnosis of dementia in their medical history and/or participants who do not master the Dutch language sufficiently will not be eligible to participate. To develop a representative control group, 90 controls will be included. Controls will be matched with a patient with COPD on smoking status (non-smoker, ex-smoker or smoker), age (SD=10 years) and education (SD=1) level according to the scoring system of the Central Bureau of Statistics (CBS) Dutch educational system.[17] Control participants with a diagnosis of COPD, asthma or dementia in their medical history are ineligible to participate, as well as participants who have Dutch language difficulties.

A subgroup of 35 patients with COPD and cognitive impairment and 35 without cognitive impairment will be included in the MRI substudy. Participants are excluded when they suffer from claustrophobia or when they have a cardiac pacemaker, cochlear implant, neurostimulator, metal fragments in the eyes and/or other electronic or metal implants.

Measures

Table 1 gives an overview of the variables assessed and instruments used.

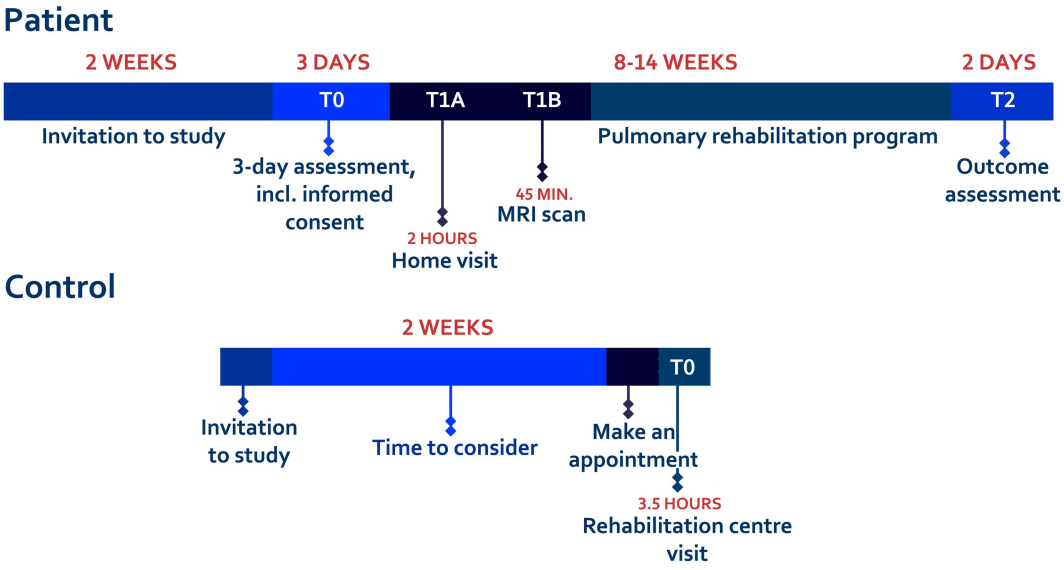

Figure 1 Study design.

Primary outcome

Our primary outcome, cognitive functioning, consists of four compound performance indices, namely psychomotor speed, memory, cognitive flexibility and planning. These will be measured with a detailed neuropsychological testing battery consisting of the following subtests:

A. A validated Dutch translation of the CFQ[18] which is a 25-item self-report inventory and comprises four main subscales: absent-mindedness, social interactions, names and words and orientation.[19] Participants are asked to indicate on a five-point scale how often they experience subjective cognitive failures. The scale ranges from 'never (0)', 'very rarely (1)', 'occasionally (2)', 'quite often (3)', to 'very often (4)'. Total scores range between 0 and 100, with a higher scores indicating more subjectively experienced cognitive failures.

B. A shortened form of the Groninger Intelligence Test (GIT)[20] will be used to determine general intelligence. Six subtasks will be administered: (1) vocabulary: measures verbal comprehension. In this subtest, 20 words of increasing difficulty are presented of which the participant has to choose the synonym out of five alternatives. The total score ranges between 0 and 20, with higher scores reflecting higher level of verbal intelligence. (2) Mental rotation: measures visualisation. This subtest requires participants to decide which of several smaller geometric shapes from a larger set are needed to fill a larger geometric figure. Total scores range between 0 and 20 with higher scores reflecting higher level of visuospatial performance. (3) Figure discovery: measures perceptual intelligence. In this subtest, the participant is shown 20 cards with silhouettes of incomplete pictures of familiar objects or animals and then has to estimate what the picture depicts. The total score ranges between 0 and 20, with higher scores reflecting higher level of perceptual intelligence. (4) Doing sums: measures numeracy. This subtest requires the participants to complete as many adding sums as possible within a time period of 1 min. The total score ranges between 0 and 32, with higher scores reflecting higher level of numeracy. (5) Analogies: measures reasoning. In this subtest, the participant has to choose one from five possibilities that correctly completes a 3×2 matrix of logical semantic relations (eg, black–white, high–low, hot...?). The total score ranges between 0 and 20, with higher scores reflecting higher level of reasoning. (6) Fluency: measures word fluency. The Animal Naming Task and the Profession Naming Task are used to assess semantic verbal fluency. These tasks require patients to generate as many names as possible within 60 seconds of animals respectively professions. Scores are determined by summing correct responses and reflect strategy-driven retrieval of information from semantic memory.

C. The Concept Shifting Test (CST)[21] which is a simple pen-and-paper test, measures concept shifting and executive functioning. This test consists of three subtasks. On each test sheet, 16 small circles are grouped in a larger circle. The small circles contain numbers, letters or both, appearing in a fixed random order. Participants are requested to cross out the items in the right order. In the final part of the test, they have to alternate between numbers (1–8) and letters (A–H). The time needed to complete each subtask and errors will be recorded. Finally, participants are presented with a condition to control for basic motor speed in which empty circles have to be marked as fast as possible in a clockwise manner. The difference between the score for the last part, corrected for basic motor speed, and the mean score for the first and second parts also corrected for basic motor speed, represent the time needed for cognitive shifting. Cognitive shifting (or mental set shifting) is considered to be part of executive functioning.[21]

Table 1 Primary and secondary outcomes in the COgnitive-PD study

	Instrument	T0	T1	T1A	T1B	T2
Primary outcome						
Cognitive functioning	Cognitive Failure Questionnaire[18]		X			
	'Groninger Intelligentie Test' (vocabulary, mental rotation, figure discovery, doing sums, analogies and fluency)[20]		X			
	Concept Shifting Test[21]		X			
	Stroop Colour-Word Interference test[22 23]		X			
	Letter Digit Substitution Test[24]		X			
	15-word learning task[25]		X			
	Behavioural Assessment of the Dysexecutive Syndrome (key-search and zoo-map test)[26]		X			
	Mini-Mental State Examination[27]		X			
	Wechsler Adult Intelligence Scale III (digit span)[30]		X			
Secondary outcomes						
Demographic characteristics						
Age	NA	X				
Educational level	CBS Dutch educational system[17]	X				
Marital status			X			
Clinical characteristics						
General psychological functioning						
Anxiety and depression symptoms	Hospital Anxiety and Depression scale[40] Beck Depression Inventory[41]	X				X
Personality	Dutch Personality Questionnaire[42]	X	X			
Psychopathology	Symptom Checklist-90[43]		X			
Coping style	Utrecht Coping List[44]	X				
Disease-specific health status	St George Respiratory Questionnaire[45]; COPD assessment test[46]	P				P
Other clinical characteristics						
Information needs	Lung Information Needs Questionnaire[47]		P			P
Arterial blood gases including PaO_2, $PaCO_2$ and SaO_2	Arterial blood gas	P				P
Medical history	Charlson comorbidity index[48]		X			
Resting transcutaneous oxygen saturation, lung function (FEV_1 and FVC) and DLCO		X				X
Use of inhaled and systemic corticosteroids, diagnosis of OSAS, oxygen therapy		X				
Smoking behaviour		X				X
Height, weight and BMI		X				X
Functional exercise capacity	6-min walk test[49]	X				X
Fatigue	Borg scale[49]	X				X
Dyspnoea	Borg scale[49]	X				X
Problem areas in daily functioning	Canadian Occupational Performance Measure[31]	P				P
Knowledge about the lung disease	CIROPD		P			P
Brain abnormalities						
Brain atrophy	Traditional MRI			P		
White matter lesions	Traditional MRI			P		
Hippocampal volume	Traditional MRI			P		
Vascular abnormalities	Traditional MRI			P		
Structural connectivity	Diffusion tensor imaging			P		
Functional connectivity	Resting state functional MRI			P		

CBS, Central Bureau of Statistics; COgnitive-PD, COgnitive-Pulmonary Disease; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NA, not applicable; OSAS, obstructive sleep apnoea syndrome; P, patient group only; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; SaO_2, oxygen saturation; T0, 3-day assessment; T1, before pulmonary rehabilitation; T1A, home visit; T1B, MRI of the brains; T2, 2-day outcome assessment; X, instrument used in both patients and controls (however, in patients assessments take place in 1 day at a single visit to the pulmonary rehabilitation centre).

D. The Stroop Colour-Word Test (SCW)[22 23] will be used to assess cognitive flexibility and is composed of three trials using word, colour and interference cards. The first card shows names of colours, printed

in black, which have to be read out loud. The second card shows patches of colours, which have to be named. The last card shows names of colours printed in incongruously coloured ink and participants are instructed to name the colour of the ink in the printed words. Errors, self-corrected errors and time of completion for all trials will be recorded. The time needed for the last card will be subtracted from the mean score for the first and second cards to obtain an interference score. This interference score can be regarded as a measure of inhibition of a habitual response (reading) which is part of the domain of executive functioning.

E. The Letter Digit Substitution Test (LDST)[24] will be used as a measure of information processing speed. A code is presented at the top of the test form, with 10 digit/letter combinations. Participants fill in digits in blank squares indexed with a letter using the code key. The key and the stimuli are the same for the oral and written versions of the LDST. The written LDST version will be administered first, immediately followed by the oral version. The number of correct substitutions made in 60 s is the dependent variable for both test versions.

F. The 15-word learning task (WLT-15)[25] visual version will be used to measure memory and verbal learning. In this test, 15 words are visually presented, one after the other, at 2 s intervals. The participants are then asked to recall as many words as possible, in a random order. This procedure will be repeated five times. When the fifth trial is completed, a fixed battery of other cognitive tests will be administered for about 20 min. After the delay, unexpectedly for the participant, the instruction will be given to recall the words learned (delayed recall). This will be followed immediately by a recognition test, involving yes/no recognition of the 15 words intermixed with 15 non-target words. Dependent variables are the total number of recalled words in the first three trials, the number of words recalled after 20 min and the number of words recognised in the recognition trial.

G. The key search of the Behavioural Assessment of the Dysexecutive Syndrome will be used as a measure of executive functioning.[26] It is claimed that this test assesses ability to plan a strategy to solve a problem (finding a key lost in a field). The score is based on a number of criteria, including whether the rater believes the strategy to be systematic, efficient and likely to be effective. A penalty is imposed for lack of speed.

H. The zoo-map test of the Behavioural Assessment of the Dysexecutive Syndrome as a measure of executive functions.[26] This is a test to assess ability independently to formulate and implement a plan (high demand condition) and to follow a preformulated plan (low demand condition). It involves plotting or following a route through a map that does not contravene a set of rules. The score is based on the successful implementation of the plan. Penalties are imposed for rule breaks and lack of speed.

I. Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE)[27] as a brief screening for global cognitive functioning. This test consists of questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction to measure global cognitive functioning. The MMSE consists of 20 questions and the maximum score to achieve is 30 points, with a higher score indicating a better cognitive performance. A score of 26–30 indicates 'normal cognitive functioning', a score of 24 or 25 'borderline normal cognitive functioning', a score below 24 'cognitive impairment'[28] and a score below 18 'severe cognitive impairment'.[29]

J. Digit span from the Wechsler Adult Intelligence Scale III (WAIS-III)[30] as a measure of short-term memory. This test consists of two parts, namely orally presented digits forward and digits backwards. Participants are required to repeat 3–9 digits forward and 2–9 digits backwards. There are two trials at each series length, and the test continues until both trials of a series length are failed. One point is awarded for each correct trial.

Secondary outcomes

Age, educational level and marital status will be obtained from the patient records. Psychological factors may influence cognitive functioning. Therefore, symptoms of anxiety and depression, personality, psychopathology, coping style and disease-specific health status will be measured using the questionnaires mentioned in table 1. Problems in daily functioning will be measured by the Canadian Occupational Performance Measure's (COPM) semistructured interview.[31] The COPM is an outcome measure designed for use by occupational therapists to assess client outcomes in the areas of self-care, productivity and leisure.[32] The CIROPD, a knowledge questionnaire developed by CIRO+, Horn will assess what persons know about COPD. The CIROPD is available from authors on request.

Conventional MRI will be analysed on brain atrophy, white matter lesions, hippocampal volume and vascular abnormalities by skilled laboratory technicians. In addition, resting state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI) will be used. In diffusion-weighted imaging (DWI), the MR signal is made sensitive to tissue water diffusion in a certain direction. In DTI, for each voxel, the diffusion-weighted signal is evaluated in several directions to which a diffusion tensor is fitted. Because in white matter the voxel diffusion coefficient is maximal in the direction parallel to the fibre orientation within that voxel, DTI is a technique to study white matter architecture.[33] fMRI specifically visualises neuronal activity-related changes in cerebral perfusion and thus provides unique insights into the localisation of cognitive functions. In rs-fMRI, no cognitive challenge is presented

and the spontaneous fluctuation of neuronal activity is assessed. Brain areas that show synchronised activity over time are functionally connected.[34] In conventional MRI, the signal intensity of a brain region reflects the local composition of the brain tissue. In connectivity studies, the signal intensity of a brain region will also provide information of the structural (DTI) and functional connections (rs-fMRI).

Planned statistical analyses

To answer objective 1, cross-sectional analyses will be used to evaluate differences in cognitive functioning in specific domains between 90 patients with COPD (stratified into GOLD stages for severity of COPD) and their matched controls. Student t test will be used for parametric distributed continuous data, Mann-Whitney U test for non-parametric distributed ordinal data and χ^2 test for categorical variables. Multivariate analyses will be used to correct for possible confounders, including comorbidities.

To limit the number of dependent variables and to improve the robustness of the underlying cognitive construct, the raw test scores will be clustered in four compound performance indices, namely psychomotor speed, memory, cognitive flexibility and planning. For all participants, the raw scores will be transformed into Z-scores (Z={x−mean}/SD).[35 36] By transforming raw scores to Z-scores, performances can be compared and individual test performances can be classified. This enables us to distinguish between impaired and non-impaired performances on the neuropsychological testing battery. Z-scores from tests that were included in each compound performance index will be averaged. The factor, psychomotor speed, which refers to the speed at which different cognitive operations can be executed, will be created from performance indices on the Stroop Colour-Word Test (initial condition), CST (the time required for the initial condition) and the Letter Digit Substitution Test (raw scores). The memory score will be derived from the total score, the maximum score and delayed recall score of the 15-WLT and the maximum score on the Digit span. The cognitive flexibility score will include the time required for the third condition of the CST (alternating letter/digit cancellation) and the time required for subtask 3 of the SCWI. Finally, planning will consist of total scores on the key research and the total scores on the first condition of the Zoo-map test. In addition, the total score of the MMSE will be used as a general cognitive measure. The sum of the six standardised subscale scores of the GIT will be multiplied by 9/6, yielding an estimate of the complete test score. This estimate will be converted into an IQ score. The sum score of the Cognitive Failure Questionnaire (CFQ) will be used as a measure of subjective cognitive functioning.

To answer objective 2, two COPD groups will be created: 'worst scoring patients with COPD differ −1 SD on the overall compound scores of the neuropsychological testing battery compared with the overall compound scores of the MAAS study and the best scoring patients with COPD differ +1 SD on the overall compound scores of the neuropsychological testing battery compared with the overall compound scores of the MAAS study.[37] Clinical characteristics (such as results of blood gases, lung function, etc) and demographic characteristics will be compared between these two groups using univariate and multivariate analyses.

To answer objectives 2–4, correlation analysis/multivariate regression analysis will be used. Potential predictors are defined as variables with a marginally significant association ($p<0.10$) with the outcome variable. Only these variables will be included in the subsequent regression analyses to determine the most important predictors. In general, effects with a two-tailed <0.05 are considered statistically significant.

To answer objective 5, cross-sectional analyses will be used to evaluate differences in brain abnormalities between patients with COPD with and without cognitive impairment. Correlation analysis/multivariate regression analysis will be used to assess the relationship between brain abnormalities and cognitive and daily functioning. Significant correlations will be included in the subsequent regression analyses.

Participants who successfully complete initial assessment and the home visit will be assessed for the first three objectives. Participants who do not complete the outcome assessment will be excluded for the fourth objective. Missing data will be processed without imputation. Post hoc tests with Bonferroni correction will be used to increase the validity of the research and to correct p values in large quantities of statistical tests. Furthermore, the data will be adjusted for gender and pack years.

Sample size and power calculation

A sample size calculation with a power of 95%, effect size=0.25 and $\alpha=0.05$ showed that 175 participants are needed to answer our first objective. Therefore, 90 patients and 90 matched controls will be included. Our secondary objectives are based on a four-point difference on the St. George's Respiratory Questionnaire. Because this concerns a clinically relevant difference, we expect greater differences on our secondary objectives, compared with our main aim. Therefore, we opted for a power of 80%. With regard to an expected drop-out rate of 10%, the sample size includes 183 patients and 90 controls.

Monitoring

The study will be monitored once a year by independent healthcare professionals from CIRO+, according to the guidelines of the Dutch Federation of University Medical Centres (NFU) and will be conducted in accordance with the Medical Research Involving Human Subjects Act (WMO).

ETHICS AND DISSEMINATION

Ethical considerations

The study is based on informed written consent, and participants can withdraw from the study at any point in time. The study is non-invasive and imposes no significant risks. Data material will be managed confidentially and anonymously.

Dissemination

Results will be disseminated through regional, national and international research conferences and in articles published in international peer-reviewed journals.

DISCUSSION

The COgnitive-PD study has several strengths and methodological considerations which are discussed below.

Strengths

The approach of our project differs considerably from other studies on neuropsychological factors in COPD by its predominant focus on cognitive functioning in specific domains. So far, in previous studies, cognitive functioning was often assessed using a single scale to measure global cognitive functioning (eg, MMSE).[10 38] The COgnitive-PD study uses a comprehensive neuropsychological testing battery and novel imaging techniques. Therefore, cognitive functioning in specific domains in patients with COPD can be adequately pictured. Next to the local composition of the brain tissue, rs-fMRI and DTI will give information of the structural connections (DTI) and functional connections (rs-fMRI). Furthermore, recruitment of participants in a pulmonary rehabilitation centre allows us to further explore the effects of domain-specific cognitive skills on pulmonary rehabilitation outcomes and daily functioning in patients with COPD. Insight in the incidence and clinical implications of cognitive impairment will help to adjust disease-management programmes and pulmonary rehabilitation to the patient's needs and capacity.

Methodological considerations

Confounding factors may influence the comparison between groups. However, we will use matching on smoking status, age and educational level as a technique to create similar groups of participants. The data will also be adjusted for confounding factors such as bronchodilator drugs, IQ level and gender. Audio and visual functions must be intact in patients with COPD and controls to obtain reliable measurements. However, whether the participant has impairment in hearing and vision will be assessed during the home visit. Furthermore, recruitment in a rehabilitation centre will provide, in particular, patients with COPD experiencing moderate to very severe limitations in daily life activities,[32 39] which may decrease the generalisability of the results to the general population of patients with COPD. Finally, due to the cross-sectional assessment of cognitive functioning, we are not able to set conclusions about causal relationships, for example, between comorbidities and cognitive functioning.

Conclusions

In conclusion, the COgnitive-PD study findings will give more insight into neuropsychological functioning in patients with COPD and shed light on the impact of cognitive impairment on pulmonary rehabilitation. This could help to adjust disease management and pulmonary rehabilitation programmes to the needs and capacity of cognitively impaired patients with COPD.

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Contributors FAHMC, DJAJ and MAS designed and established the study. All the authors contributed to the writing of this manuscript, read and approved the final manuscript.

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Competing interests None.

Ethics approval The study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035) and is registered in the Dutch trial register.

Provenance and peer review Not commissioned; externally peer reviewed.

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