




# The Association Between Cognitive Functions and Psychological Factors in Patients with Severe COPD

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**Purpose:** Patients with COPD experience anxiety, depression, and stress more frequently than in the age and gender-matched general population. This cross-sectional study aimed to examine the relationship between cognitive functions and the psychological factors of anxiety, depression and stress among patients with COPD.

**Patients and Methods:** Between January 2021 and January 2023, patients with severe COPD were recruited, along with age-matched controls. Participants completed the Hospital Anxiety and Depression Scale (HADS) and the Perceived Stress Scale (PSS). The Montreal Cognitive Assessment (MoCA), a continuous reaction time test (CRT), and a driving simulator were used to assess cognitive impairment. Hierarchical multiple linear regression analyses were used to explain the variance of the correlations.

**Results:** In total, 80 patients (mean age = 64yrs) and 22 controls (mean age = 61yrs) participated in the study. Patients reported significantly higher levels of psychological symptoms compared to the controls ( $p \leq 0.001$ ). We found no differences in anxiety ( $p = 0.31$ ), depression ( $p = 0.66$ ) and stress ( $p = 0.37$ ) between patients with and without cognitive impairment. However, stress showed to be a significant predictor of decreased attention (higher stress score resulted in decreasing CRT-index, indication a reduced stability in reaction time) ( $p = 0.02$ ). Psychological factors did not explain additional variance in cognitive functions beyond sociodemographic factors such as age and sex.

**Conclusion:** Psychological symptom levels are higher in COPD than controls and perceived stress among patients with COPD appears to be associated with decreased attention. However, psychological factors in general did not appear to contribute to the variance in cognitive functions beyond sociodemographic, physical, and self-perceived symptoms.

**Keywords:** chronic obstructive pulmonary disease, cognitive impairment, Montreal Cognitive Assessment, anxiety, depression, stress

## Introduction

COPD is a complex and multifactorial disease and comorbidities are more common in patients with COPD than in the age and gender-matched general population.<sup>1,2</sup> To fully characterize the clinical spectrum of COPD, identification, comprehension, and assessment of all comorbidities in COPD are required.<sup>3</sup> Some of the prevalent comorbidities include cardiovascular disease,<sup>4</sup> osteoporosis,<sup>5</sup> lung cancer,<sup>6</sup> type 2 diabetes<sup>7</sup> and cognitive impairment (CI)<sup>8</sup> as well as obstructive sleep apnea (OSA), which is linked to CI.<sup>9</sup>

Cognitive functions such as memory and learning, word finding, perception, attention, executive function, and motor function and can all be negatively impacted in people with COPD.<sup>1</sup> Neuropsychological tests are used to examine cognitive functions, for example generic tests like Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE) as well as more domain-specific tests such as Stroop Color-Word Test or Wechsler Memory Scale.<sup>10,11</sup> CI is associated with age and appears in some studies to be more common in male sex.<sup>12,13</sup> Some studies<sup>11,14</sup> show an association between hypoxemia and cognitive functions. Alcohol consumption and deterioration of vision and hearing also affects the cognitive functions.<sup>12,15,16</sup>

In patients with COPD, CI reduces the level of function in everyday life and can lead to poor adherence with both medication and oxygen therapy.<sup>17,18</sup> Lack of adherence with inhalation therapy in patients with COPD increases the risk of acute exacerbations.<sup>19</sup> Studies have looked into the prevalence estimates of CI in COPD, with conflicting results ranging from 10.4% to 77%.<sup>20,21</sup> Furthermore, several studies<sup>11,22</sup> have examined and found an association between the forced expiratory volume in 1 s (FEV<sub>1</sub>) and CI, while other studies<sup>13,23</sup> show no correlation between FEV<sub>1</sub> and CI.

However, a connection between COPD-related symptoms and CI may be explained by FEV<sub>1</sub> or FVC, but not exclusively so. A study by von Siemens et al,<sup>24</sup> using the screening instrument DemTect for evaluation of CI, demonstrated that it was not solely FVC but instead self-perceived disease-specific quality of life measured by St George's respiratory questionnaire (SGRQ) that was associated with CI. Patients with a similar degree of FEV<sub>1</sub> reduction may experience breathlessness and other COPD-related symptoms differently, and as the Nishimura et al study demonstrated,<sup>25</sup> lung function does not accurately predict the perceived severity of dyspnea and other COPD-related symptoms.

The patients' mental health may have an impact on self-reported COPD-related symptoms or vice versa; COPD-related symptoms may have an impact on the patients' mental health, which may then have an impact on their cognitive functions. It is known that patients with COPD experience anxiety, depression, and stress more frequently than in the age and gender matched general population,<sup>26</sup> as well as more frequently than in patients with conditions such as ischemic heart disease, diabetes, cerebral infarctions, and cancer.<sup>27</sup> Smoking, which is the primary risk factor for developing COPD, at least in the Western World, is associated with depression<sup>28</sup> and CI.<sup>29</sup> Psychological factors can also affect the treatment, compliance and outcome in patients with COPD.<sup>2</sup>

It is difficult to assess whether sociodemographic factors, physical or self-perceived disease-related symptoms, or a generalized state of poor health are more likely to contribute to CI than COPD itself. Furthermore, CI might primarily be carried forward due to poor mental health. Therefore, we aimed to study the relationship between cognitive functions and the psychological factors of anxiety, depression and stress among patients with COPD.

## Materials and Methods

In a cross-sectional study conducted between January 2021 and January 2023, patients with COPD were enrolled from the Outpatient Clinic of Respiratory Diseases at a Danish University Hospital. Age-matched controls were chosen as a reference group.

### Study Population

Patients were eligible to participate in the study if they had severe or very severe COPD (forced expiratory volume in one second (FEV<sub>1</sub>) <50% of predicted) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 classification.<sup>30</sup> According to some research,<sup>31</sup> CI is associated with disease severity and we were interested in learning more about the factors that contribute to CI in severe COPD. We chose this group to be sure there was some prevalence of CI. Due to the magnitude of the test battery, we could only test a limited number of patients while still trying to test as homogeneous a group as feasible.

Eligible patients had to be within the age span of 40 to 75 years, possess a valid driver's license, and be without COPD exacerbations in the previous three weeks. Previous studies<sup>32–34</sup> using driving simulators have applied the exclusion criteria of not holding a valid driver's license, due to minimization of training bias in the results. The non-COPD reference group included volunteers from the general public who reacted to adverts on social media as well as family members or friends of the included patients with COPD.

Participants were excluded from the study if they met at least one of the following criteria: 1) were physically unable to operate the driving simulator; 2) needed oxygen therapy; 3) had a history of obstructive sleep apnea; 4) consumed a large amount of alcohol (>21 units per week for men; >14 units per week for women); 5) had uncorrected vision or hearing loss; 6) had serious uncontrolled comorbidities; 7) did not read or understand Danish.

We decided to exclude participants in oxygen therapy, as their oxygen levels were "artificially" (medically) ameliorated. Participants with OSA were excluded because we aimed to explore the treatment effect of undiagnosed OSA on cognitive functions over time. We excluded participants with high alcohol consumption and poor vision/hearing abilities as it may compromise the validity of the cognitive tests.

Prior to data collection, informed consent was obtained from each participant. The Southern Denmark Regional Committee on Health Research Ethics (S-20190082) and the Danish Data Protection Agency both accepted the study. The study was registered with the Open Patient Data Explorative Network (OPEN), Odense University Hospital (OP\_1159), and [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04458038) in compliance with the Declaration of Helsinki.

## Data Collection

KKH, who had received training in using the cognitive assessment battery, collected the data. Patients were examined in a quiet room free from disturbance. It took between two and three hours to complete the examination and involved answering questionnaires, clinical evaluation, and cognitive assessment. To minimize the influence of exhaustion on the performance during cognitive assessment, we performed the cognitive tests first, followed by the clinical evaluation and questionnaires. We finished with a collection of record data.

## Questionnaires

Participants completed the COPD Assessment Test (CAT)<sup>35</sup> and the modified Medical Research Council (mMRC-scale) dyspnea scale,<sup>36</sup> and provided information about their age, sex, cohabitation, education level (International Standard Classification of Education 2011),<sup>37</sup> employment status and smoking history. Medical records were used to gather data on the comorbidities including Charlson Comorbidity Index Score and exacerbation history of the patients. Participants completed the Epworth Sleepiness Scale (ESS)<sup>38</sup> and their mental health was examined using the Hospital Anxiety and Depression Scale (HADS)<sup>39,40</sup> and the Perceived Stress Scale (PSS).<sup>41</sup>

## Clinical Assessment

Data on forced vital capacity (FVC) (L), FVC% predicted, FEV<sub>1</sub>(L), FEV<sub>1</sub>% predicted, and FEV<sub>1</sub>/FVC were collected. A CardioRespiratory Monitor (CRM), NOX T3™ (ResMed, Denmark) is handed out to the participant, along with instructions on how to use it at home the same night and return it the next day. The CRM is used to assess respiratory effort, nasal airflow, pulse, and oxygen saturation during sleep.<sup>42</sup>

## Cognitive Assessment

A battery of neuropsychological tests, including the Montreal Cognitive Assessment test (MoCA),<sup>43,44</sup> was used to evaluate cognitive functions. All participants were divided into groups based on their overall MoCA score, with a score of <26 indicating CI and a score of ≥26 indicating no CI. According to Nasreddine et al, the cut-off value of 26 yields the best balance between sensitivity and specificity.<sup>43</sup> Visuospatial ability, executive functioning, attention, language, and short-term memory through delayed recall are the five selected MoCA domains that were evaluated.

A 20-minute driving simulator test was also conducted.<sup>45</sup> The standard deviation (SD) of the car's distance from the center of the road and the ability to press a button on the steering wheel when the number "2" appeared on the screen (average response time in seconds) were used to assess participants' perception and attention.<sup>11</sup> Additionally, participants completed the Continuous Reaction Times (CRT) test,<sup>46</sup> which is created to assess sustained attention and attention stability, as well as reaction time, in cirrhosis patients. CRT-index >1.9 is considered normal.<sup>46</sup>

## Statistics

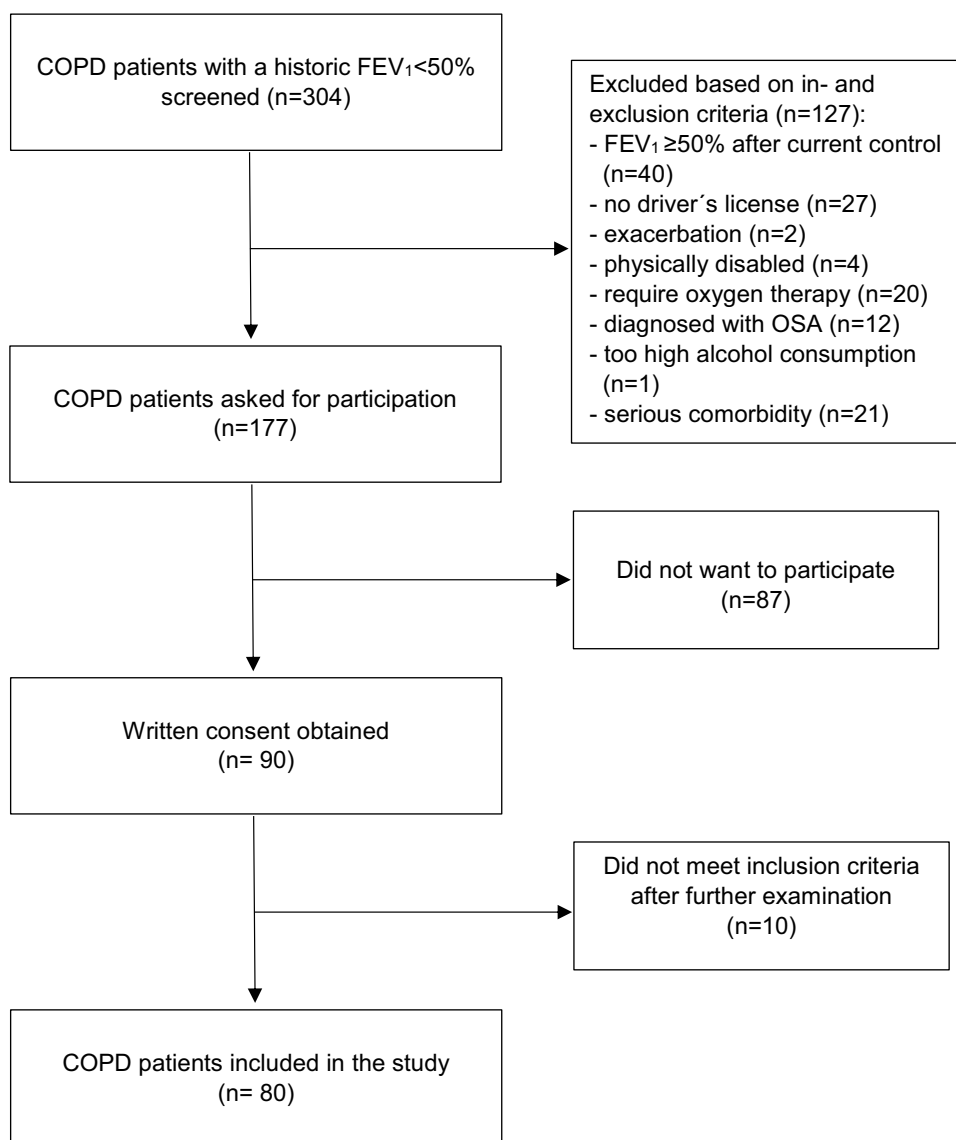
Continuous data were checked for normal distribution and descriptive analyses were made. To compare the mean value of the results that were normally distributed between the COPD and control group and the CI group and the group without CI, parametric unpaired t-tests were utilized. Chi<sup>2</sup> was used for categorical data and non-parametric Mann Whitney *U*-tests were used for not normally distributed continuous data.

Whether psychological factors (anxiety, depression and stress) predicted cognitive function better than sociodemographic (age, sex and years of education), and physical factors (FEV<sub>1</sub>, sleep apnea and smoking), or self-perceived COPD symptom burden (CAT score) were examined using hierarchical multiple linear regression analysis. Independent variables that were not normally distributed were converted into logarithmic before regression analyses were conducted. The hierarchical regression analyses consisted of four steps and in each step, unadjusted and  $\Delta R^2$  estimates were reported (including Likelihood-ratio test).

A 5% significance level was in all cases used to determine statistical significance. An estimated range with a 95% confidence level was provided. The sample size calculation based on MoCA scores (values from relevant studies),<sup>31,47</sup> with a mean of 26, power 0.9, difference 2, SD 2, alpha 0.05 and a patient–control ratio of 5:1, showed a need for a minimum of 65 patients and 13 controls. Data was entered into Research Electronic Data Capture (REDCap), a secure web application that is designed to handle both online and offline data collection for research studies and operations. Statistical analysis was performed using Stata version 17.0.

## Results

Out of 177 eligible patients with severe COPD, 80 (53% male) were included in this study. The impact of COPD symptoms on physical functioning, too frequent hospital visits and lack of motivation were most commonly stated as reasons for not participating. Twenty-two age-matched controls (32% male) were also included. The inclusion process is illustrated in the study flowchart (Figure 1). Fifty-eight (73%) and twenty-two (27%) patients were spirometrically categorized as GOLD 3 and GOLD 4, respectively. There were several statistically significant differences in covariates between patients and controls,



**Figure 1** Study flowchart of the inclusion process.

**Abbreviations:** FEV<sub>1</sub>, Forced Expiratory Volume in 1 second, % of predicted; OSA, Obstructive Sleep Apnea.

including sociodemographic, physical and psychological factors (Table 1). We found 56 patients (70%) with undiagnosed OSA and/or ND at the time of recruitment. These patients were not excluded but instead we adjusted for OSA and/or ND in the analysis.

## Characteristics of Patients with and without CI on Psychological Factors

As shown in Table 2, we did not find any statistically significant differences in anxiety, depression and stress between patients with CI and without CI.

## Hierarchical Regression Analyses

The hierarchical multiple-regression analysis is displayed in Table 3.

### Cognitive Impairment Based on MoCA Score

Results from the analyses showed that in the first and second step of the model, the sociodemographic factors, age and years of education, were the only significant predictors of CI, explaining 17.5% of the variance in outcome. Higher age and less years of education were associated with more CI. Only age continued being statistically significant through all four steps, adding another 3.3% to the variance. Neither physical factors, self-perceived COPD-symptom burden nor psychological factors explained any additional variance of CI based on MoCA score.

**Table 1** Baseline Characteristics of Patients with COPD and Age-Matched Controls

	COPD Patients (n=80)	Controls (n=22)	p
Age (yrs), mean (SD)	64 (7)	61 (9)	0.13
Sex (male), n (%)	42 (53)	7 (32)	0.09
Cohabitation, n (%)			
Living alone	27 (34)	1 (5)	<0.01
Living with partner	53 (66)	21 (95)	
Years of education, mean (SD)	12 (3)	15 (3)	<0.01
Employment status, n (%)			
Not working	21 (26)	0 (0)	<0.01
Working	22 (28)	12 (55)	
Pensioner	37 (46)	10 (45)	
Smoking, n (%)			
Smoker	30 (37)	1 (5)	<0.001
Former	50 (63)	9 (41)	
Never	0 (0)	12 (54)	
FEV <sub>1</sub> , % predicted, mean (SD)	35 (8)	99 (11)	<0.001
mMRC (0–4), median (IQR)	2 (2–3)	0 (0–0)	<0.001
CAT score (0–40), mean (SD)	18 (7)	–	
Obstructive Sleep Apnea and/or ND, n (%)	56 (70)	6 (27)	<0.001
ESS (0–24), mean (SD)	5 (3)	4 (2)	0.05
Charlson Comorbidity Index Score, median (IQR)	1 (1–2)	0 (0–0)	<0.001
Mental health disorder, n (%)	10 (13)	1 (5)	0.29
HADS (0–42), mean (SD)	8 (6)	2 (2)	0.00
HADS-Anxiety (0–21), mean (SD)	5 (4)	2 (2)	<0.001
HADS-Depression (0–21), mean (SD)	3 (3)	1 (1)	0.00
PSS (0–40), mean (SD)	12 (7)	4 (3)	0.00

**Notes:** Continuous variables are specified as mean (SD) and categorical variables as number (%). mMRC and Charlson Comorbidity Index Score are not normal distributed and therefore we use median (IQR). Using parametric unpaired t-test for continuous normally distributed data. Using nonparametric Mann Whitney U-test for not normal distributed data. Using Chi-squared test for categorical data.

**Abbreviations:** FEV<sub>1</sub>, Forced Expiratory Volume in 1 second, % of predicted; mMRC, modified Medical Research Council dyspnea scale; CAT score, COPD Assessment Test score; ND, Nocturnal Desaturation; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale.

**Table 2** Characteristics of Patients with COPD with CI (MoCA Score <26) and without CI (MoCA Score 26–30)

	CI (n=32)	No CI (n=48)	p
Age (yrs), mean (SD)	67 (8)	62 (6)	<0.01
Sex (male), n (%)	15 (47)	27 (56)	0.41
Cohabitation, n (%)			
Living alone	9 (28)	18 (38)	0.39
Living with partner	23 (72)	30 (62)	
Years of education, mean (SD)	12 (3)	13 (3)	0.02
Employment status, n (%)			
Not working	7 (22)	14 (29)	<0.01
Working	3 (9)	19 (40)	
Pensioner	22 (69)	15 (31)	
Smoking, n (%)			
Smoker	12 (38)	18 (38)	1.00
Former	20 (62)	30 (62)	
Never	0 (0)	0 (0)	
FEV <sub>1</sub> , % predicted, mean (SD)	36 (8)	34 (9)	0.27
mMRC (0–4), median (IQR)	4 (3–4)	3 (2–4)	0.02
CAT score (0–40), mean (SD)	19 (6)	16 (7)	0.047
Obstructive sleep apnea and/or ND, n (%)	20 (63)	36 (75)	0.23
ESS (0–24), mean (SD)	5 (3)	5 (3)	0.89
Charlson Comorbidity Index Score, median (IQR)	1 (1–2)	1 (1–2)	0.65
Mental health disorder, n (%)	3 (9)	7 (15)	0.49
HADS (0–42), mean (SD)	9 (6)	8 (6)	0.40
HADS-Anxiety (0–21), mean (SD)	6 (4)	5 (4)	0.31
HADS-Depression (0–21), mean (SD)	3 (3)	3 (3)	0.66
PSS (0–40), mean (SD)	13 (7)	12 (8)	0.37

**Notes:** Continuous variables are specified as mean (SD), not normally distributed variables as median (IQR) and categorical variables as number (%). Using parametric unpaired *t*-test for normally distributed data. Using nonparametric Mann Whitney *U*-test for not normally distributed data. Using Chi-squared test for categorical data.

**Abbreviations:** CI, cognitive impairment; MoCA, Montreal Cognitive Assessment; FEV<sub>1</sub>, Forced Expiratory Volume in one second, % of predicted; mMRC, modified Medical Research Council dyspnea scale; CAT score, COPD Assessment Test score; ND, Nocturnal Desaturation; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale.

### Sustained Attention and Attention Stability Based on CRT-Index

The first three steps of the model explained 16.8% of the variance in attention and attention stability based on CRT-index, with sex as the only statistically significant predictor. Being a man was associated with better attention (higher CRT-index score indicating higher stability in reaction time) compared to being a woman. Adding psychological factors to the model in step four explained additionally 8.8% ( $p = 0.03$ ) of the variance in CRT-index score, with stress as the only significant predictor. A one-point increase in PSS score resulted in decreasing CRT-index, indicating a reduced stability in reaction time.

### Perception and Attention Based on Driving Data

The first step of the model, including sociodemographic information, explained 39.4% of the variance in perception and attention measured by SD from center of the road in the driving test. Age and sex were statistically significant predictors and remained the only significant predictors through all subsequent steps in the model. Higher age and being a woman were associated with higher SD from center of the road and thereby worse perception and attention. No additional variance in SD from center of the road could be explained by physical factors (step 2), self-perceived COPD symptom burden (step 3), or psychological factors (step 4).

Concerning the outcome of average response time, sociodemographic information and physical factors accounted for 25.3% of the variance (steps 1 and 2), with age and sex as statistically significant predictors. Higher age and being a woman were associated with higher average response time indicating longer reaction time. Adding self-perceived COPD symptom

**Table 3** Hierarchical Multiple Regression Analyses – Associations of Sociodemographic, Physical and Self-Perceived COPD Symptoms as Well as Psychological Factors and Cognitive Functions in Patients with COPD

Model	Predictors	Cognitive Outcome Variables																			
		Cognitive Impairment (MoCA Score) n=80					Attention (CRT-Index) n=80					Perception and Attention (SD from Center of the Road) n=78					Perception and Attention (Average Response Time in Sec.) n=78				
		$\beta$	<i>p</i>	$R^2$	$\Delta R^2$	<i>p</i>	$\beta$	<i>p</i>	$R^2$	$\Delta R^2$	<i>p</i>	$\beta$	<i>p</i>	$R^2$	$\Delta R^2$	<i>p</i>	$\beta$	<i>p</i>	$R^2$	$\Delta R^2$	<i>p</i>
Step 1				0.156 <sup>a</sup>	-	-			0.140 <sup>a</sup>	-	-			0.394 <sup>b</sup>	-	-			0.239 <sup>b</sup>	-	-
	Age	-0.099	<0.01				0.006	0.57				1.079	0.00				1.030	0.00			
	Sex (reference female)	0.173	0.72				0.449	<0.01				0.267	0.00				0.815	0.03			
	Years of education	0.185	0.03				0.039	0.13				0.934	0.10				1.005	0.75			
	Constant term	29.908					0.947					0.027					0.453				
Step 2				0.175 <sup>c</sup>	0.019	0.63			0.155 <sup>c</sup>	0.015	0.7			0.408 <sup>b</sup>	0.014	0.60			0.253 <sup>a</sup>	0.014	0.68
	Age	-0.088	0.01				0.004	0.72				1.076	0.00				1.029	0.00			
	Sex (reference female)	0.206	0.67				0.459	<0.01				0.275	0.00				0.817	0.04			
	Years of education	0.193	0.02				0.036	0.18				0.933	0.10				1.005	0.75			
	FEV <sub>1</sub> , % predicted	-0.013	0.67				0.005	0.58				1.018	0.22				1.003	0.61			
	Currently smoker (reference no smoking)	0.532	0.33				-0.043	0.80				0.956	0.87				0.978	0.84			
	Sleep apnea (reference no OSA and/or ND)	0.440	0.42				0.149	0.39				0.950	0.85				0.899	0.33			
	Constant term	29.005					0.835					0.019					0.460				

(Continued)

Table 3 (Continued).

		Cognitive Outcome Variables																			
		Cognitive Impairment (MoCA Score) n=80					Attention (CRT-Index) n=80					Perception and Attention (SD from Center of the Road) n=78					Perception and Attention (Average Response Time in Sec.) n=78				
Model	Predictors	$\beta$	<i>p</i>	$R^2$	$\Delta R^2$	<i>p</i>	$\beta$	<i>p</i>	$R^2$	$\Delta R^2$	<i>p</i>	$\beta$	<i>p</i>	$R^2$	$\Delta R^2$	<i>p</i>	$\beta$	<i>p</i>	$R^2$	$\Delta R^2$	<i>p</i>
Step 3				0.191 <sup>c</sup>	0.016	0.20			0.168	0.013	0.26			0.416 <sup>b</sup>	0.008	0.30			0.302 <sup>b</sup>	0.049	0.02
	Age	-0.087	0.01				0.004	0.69				1.076	0.00				1.028	0.00			
	Sex (reference female)	0.132	0.79				0.438	<0.01				0.267	0.00				0.838	0.07			
	Years of education	0.167	0.054				0.028	0.30				0.923	0.07				1.015	0.37			
	FEV <sub>1</sub> , % predicted	-0.025	0.42				0.001	0.88				1.013	0.42				1.008	0.21			
	Currently smoker (reference no smoking)	0.695	0.22				0.003	0.99				1.022	0.94				0.921	0.46			
	Sleep apnea (reference no OSA and/or ND)	0.503	0.36				0.167	0.33				0.971	0.91				0.881	0.23			
	CAT score	-0.049	0.23				-0.014	0.28				0.980	0.33				1.017	0.03			
	Constant term	30.480					1.254					0.034					0.273				
Step 4				0.208	0.017	0.63			0.256 <sup>c</sup>	0.088	0.03			0.437 <sup>b</sup>	0.021	0.43			0.332 <sup>a</sup>	0.03	0.33
	Age	-0.093	0.01				0.0003	0.98				1.078	0.00				1.028	0.00			
	Sex (reference female)	0.216	0.67				0.440	<0.01				0.282	0.00				0.820	0.047			
	Years of education	0.165	0.059				0.026	0.32				0.924	0.07				1.014	0.40			



	FEV <sub>1</sub> , % predicted	-0.036	0.28				0.003	0.79							1.014	0.39					1.010	0.13					
	Currently smoker (reference no smoking)	0.798	0.18				-0.037	0.83							1.061	0.84						0.893	0.32				
	Sleep apnea (reference no OSA and/or ND)	0.512	0.36				0.232	0.17							1.008	0.98						0.890	0.27				
	CAT score	-0.059	0.22				-0.001	0.92							0.975	0.28						1.022	0.02				
	HADS-Anxiety	0.003	0.98				0.060	0.10							1.094	0.13						1.011	0.64				
	HADS-Depression	-0.166	0.27				-0.030	0.50							0.968	0.64						1.028	0.33				
	PSS	0.046	0.43				-0.041	0.02							0.978	0.45						0.981	0.10				
	Constant term	31.234					1.522								0.027							0.258					

**Notes:** <sup>a</sup> $p < 0.01$ , <sup>b</sup> $p < 0.001$ , <sup>c</sup> $p < 0.05$ . Results from hierarchical regression analysis depicting the contribution of mental health to cognitive functions. In a stepwise regression, sociodemographic were controlled for in the first model. In the second model, physical variables were added, and self-perceived COPD symptoms were added in the third model. In the final model, mental health were added. Models explained variances are reported as  $R^2$  and  $\Delta R^2$ , which are the difference in  $R^2$  between the steps. Using Likelihood-ratio test to examine significance level of  $\Delta R^2$ . Driving outcome variables are not normally distributed and therefore regression analyses are made with log-transformed data but coefficients are back transformed via exponential function.

**Abbreviations:** MoCA, Montreal Cognitive Assessment; CRT-index, Continuous Reaction Time Index; SD, standard deviation; FEV<sub>1</sub>, Forced Expiratory Volume in one second, % of predicted; OSA, Obstructive Sleep Apnea; ND, nocturnal desaturation; CAT score, COPD Assessment Test score; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale.

burden in step three explained an additional 4.9% of the variance ( $p = 0.02$ ), with CAT score as a significant predictor. Adding psychological factors to the model in step four did not result in a significant change in the model.

## Supplementary Subgroup Analysis

In a subgroup analysis dividing the patients into three groups of driving time (<10, 10–19.99 and 20 minutes), we did not find any statistically significant differences in anxiety, depression and stress between the groups ([Table S1](#)).

## Discussion

The results of the present study showed that patients with severe COPD reported statistically significantly higher levels of anxiety, depression and stress symptoms compared to their age-matched non-COPD controls, which concurs with findings from multiple other studies.<sup>26,48</sup> However, when comparing patients with CI to patients without CI, there were no statistically significant differences in psychological symptoms between groups. Furthermore, measures of psychological factors did not contribute to the variance to a greater extent than sociodemographic and physical factors as well as self-perceived COPD symptom burden. Contrarily, sociodemographic factors like age and sex appeared to be significantly better to explain the variance of cognitive functions compared to psychological factors. However, based on the CRT test, stress showed to be a statistically significant predictor of decreased attention, because a one-point increase in PSS score resulted in decreasing CRT-index, indicating a reduced stability in reaction time.

## Anxiety and Depression in Patients with CI

Several studies<sup>49–54</sup> examining patients with COPD and cognitive functions based on MoCA have reported results on psychological factors like anxiety and depression. However, some of these studies<sup>49,51,54</sup> are using other psychological tests than HADS or use a MoCA cut-off value of 21 to identify CI.<sup>52</sup> We found only one study,<sup>53</sup> with a HADS mean anxiety (HADS-A) and depression (HADS-D) score and with diagnosed CI (based on a MoCA cut off value of 26), that showed no statistically significant differences in mean anxiety (HADS-A) or depression (HADS-D) score between patients with CI and without CI, similarly to the findings in our study. Compared to our study, the study by Andrianopoulos et al<sup>53</sup> had a lower sample size (52 patients vs 80 patients) and a higher average age (68 vs 64 years), but a similar prevalence of CI (40%) and a nearly identical mean MoCA score (25.3 vs 26.0). None of the studies<sup>49–54</sup> examined stress.

It is possible that patients with severe COPD may already have such low levels of functioning and are so affected by psychological factors that the cognitive decline is “drowning” because of dire circumstances of living with COPD. This may explain why there was no statistically significant difference in anxiety and depression between those with and without CI. Furthermore, if we had used more COPD-specific measures of anxiety and depression such as The COPD-Anxiety-Questionnaire,<sup>55,56</sup> we may have seen a greater association between psychological factors and cognitive function. Additionally, patients with COPD who have the resources to take part in comprehensive studies may receive more support from their partners and/or network or are better to cope with CI and psychological symptoms, which means that they have less of an impact on one another.

## The Association Between Stress and Attention Based on CRT

Our hierarchical multiple-regression analyses showed that when we added psychological factors to the model, stress was the strongest and only statistically significant predictor. A study by Phibbs et al<sup>57</sup> has examined the influence of perceived stress on response time (inconsistent), and similarly to our study, this study<sup>57</sup> also found a positive, statistically significant association between perceived stress and response time. Research suggests that response time potentially serve as an indicator of CI,<sup>58</sup> and because stress affects response time, we must include stress when researching cognitive processes. Therefore, it would be preferable to adjust for stress when using neuropsychological testing. Similar to some studies,<sup>12,13,59</sup> our results also showed that age and sex are strong predictors of CI, with older age and being a woman linked to a decline in cognitive functions.

## Clinical Implications

In our present study, we did not find that patients with CI were at risk of psychological problems compared to patients without CI. Therefore, CI may not necessarily indicate the need for psychological testing. On the other hand, psychological symptoms do not automatically warrant a neuropsychological test. However, because both psychological and cognitive symptoms are often highly prevalent in patients with severe COPD,<sup>26,49</sup> screening for both should be included in routine standard care. If using CRT as a neuropsychological test, the individual level of stress should be addressed when interpreting test results.

As no consensus exists regarding which neuropsychological tests are most clinically relevant, reliable and feasible to use, future studies of cognitive functions in patients with COPD should focus on examining these aspects.

## Strength and Limitations

The relatively low rate of missing data across a broad test battery, which included data on cognitive assessment, physical and mental health in our study is a strength. The internal validity was increased by the first author (KKH), carrying out all examinations and maintaining and evaluating the data.

The patient inclusion rate of 45% is a limitation of the study. Although the cognitive functions of those who declined to participate in the study are unknown, their age and FEV<sub>1</sub> were similar to those of the patients who were included (Table S2). Dyspnea, lack of physical strength, lack of motivation, and too frequent hospital visits were given as reasons for declining participation. Patients with mental excess may be more likely to take part in a two- to three-hour examination. Therefore, we cannot rule out the risk that our study contained selection bias. Furthermore, we are aware of the risk that the exclusion of individuals without a driver's license might have resulted in biased selection of patients with better cognitive function.

## Conclusions

In our study, patients with severe COPD reported statistically significantly higher levels of anxiety, depression, and perceived stress symptoms compared to non-COPD controls of comparable age. However, when looking only at patients with COPD, there were no statistically significant differences in psychological symptoms between individuals with and without CI. While stress appeared to be a statistically significant predictor of diminished attention measured by CRT, psychological factors in general did not contribute to the variance in cognitive functions beyond sociodemographic, physical, and self-perceived symptoms in COPD.

## Abbreviations

CAT, COPD Assessment Test; CI, Cognitive Impairment; COPD, Chronic Obstructive Pulmonary Disease; CRM, CardioRespiratory Monitor; CRT, Continuous Reaction Time test; ESS, Epworth Sleepiness Scale; FEV<sub>1</sub>, Forced expiratory volume in 1 second; FVC, Forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; IQR, Interquartile Range; mMRC, Modified Medical Research Council dyspnea scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; OPEN, Open Patient data Explorative Network; OSA, Obstructive Sleep Apnea; PSS, Perceived Stress Scale; SD, Standard deviation.

## Data Sharing Statement

If interested, data can be shared upon request with the corresponding author.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article was submitted; and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in the present work.

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