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Schure, Mark B. , Soo Borson, Huong Q. Nguyen, Emily H. Trittschuh, Stephen M. Thielke, Kenneth C. Pike, Sandra G. Adams, and Vincent S. Fan. "Associations of cognition with physical functioning and health-related quality of life among COPD patients." *Respiratory Medicine* 114 (May 2016): 46-52. DOI: [10.1016/j.rmed.2016.03.005](#).

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# Associations of cognition with physical functioning and health-related quality of life among COPD patients

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## Abstract

### Background:

Neurocognitive impairment has been described in COPD patients, but little is known about its relationship with physical functioning and health-related quality of life (HRQL) in this chronically ill patient group.

### Methods:

301 stable COPD patients completed the Trail Making Test (TMT-A: psychomotor speed and TMT-B: executive control); 198 patients completed the Memory Impairment Screen (MIS). Standardization of TMT-A and TMT-B scores to a normative population yielded classifications of normal, borderline, or impaired cognitive status. Using multivariable regression, we examined the relationship between the TMT-A, TMT-B, and MIS with physical functioning (physical activity, 6-min walk test, and grip strength) and health-related quality of life (HRQL) measured with the Chronic Respiratory Questionnaire and the SF-36.

### Results:

Nearly 30% of patients had either borderline or impaired cognition on the TMT-A or TMT-B. Adjusted models indicated that those with either borderline or impaired cognitive functioning had weaker grip strength (TMT-A borderline:  $\beta = -2.9$ ,  $P < 0.05$ ; TMT-B borderline:  $\beta = -3.0$ ,  $P < 0.05$ ; TMT-B impaired:  $\beta = -2.5$ ,  $P < 0.05$ ) and lower scores on the mental health component summary score (MCS-SF-36 HRQOL) measure (TMT-A impaired:  $\beta = -4.7$ ,  $P < 0.01$ ). No adjusted significant associations were found for other physical functioning measures or the other HRQL measures. Impaired memory showed a significant association only with the MCS scale.

### Conclusions:

Cognitive function was not associated with most standard indicators of physical function or most measures of HRQL in COPD patients. Both TMT-A and TMT-B were associated with weaker grip strength, and the TMT-A and MIS with poorer mental health.

#### Keywords:

Cognition  
COPD  
Physical functioning  
Quality of life  
Physical activity  
Affective symptoms  
Motor strength

Abbreviation: 6MWT, 6-min walk test; BMI, Body Mass Index; BODE, Body-mass index, Obstruction, Dyspnea, and Exercise; CCI, Charlson Comorbidity Index; CRQ, Chronic Respiratory Questionnaire; FEV<sub>1</sub>%, Forced Expiratory Volume in one sec-ond, percent; HADS, Hospital Anxiety and Depression Survey; HRQOL, Health Related Quality of Life; MCS, Mental Component Summary Score; MIS, Memory Impairment Screen; mMRC, Modified Medical Research Council; PCS, Physical Component Summary Score; PHQ, Patient Health Questionnaire; TMT-A, Trail Making Test, Part A; TMT-B, Trail Making Test, Part B.

## 1. Introduction

In addition to declines in physical functioning, some persons with chronic obstructive pulmonary disease (COPD) suffer from substantive deficits in cognitive functioning [1,2], and COPD increases the risk of cognitive decline over time [3]. Though the basis for cognitive impairment in COPD is not fully understood [4–8], older adults with both COPD and diminished cognitive functioning have substantially higher hospitalization and mortality rates compared to those with either condition alone [9]. There is also evidence that cognitive impairment

may adversely affect other COPD outcomes including quality of life [10].

The Trail Making Tests A (TMT-A, assessing psychomotor speed) [11] and B (TMT-B, assessing executive control function) [12] are standard neuropsychological measures that are sensitive to cognitive decline among patients [13–17] and can be easily-administered screening tests. Both tests are influenced by age and education and can be affected by other factors such as gender and race; thus, standardizing scores on these tests is an important step to identify those whose performance indicates true cognitive impairment. Although the TMTs have been used to measure changes in cognitive functioning among COPD patients undergoing rehabilitation [18,19], all identified studies have analyzed the time to completion without standardizing for age and education. The omission of standardization may result in associations that can be confounded by factors unrelated to disease. Neither of the Trails tests addresses memory functioning, a key domain within the spectrum of cognitive activities. The Memory Impairment Screen (MIS) is a rapid screening test of memory encoding and retrieval [20].

Our goal was to examine the association of simple tests of cognitive functioning with standard measures of disease activity in COPD patients and to determine whether cognitive performance is independently associated with physical function, psychological symptoms, and health-related quality of life (HRQOL) among COPD patients after adjustment for disease severity. Based on existing evidence [21], we hypothesized that worse cognitive functioning, standardized for age, education, gender and race, would be associated with greater disease severity and poorer physical functioning, as measured by the six-minute walk test (6MWT), total steps per day, and grip strength. Similarly, we hypothesized that poorer cognition would be associated with lower general and disease specific HRQOL, as measured with the Medical Outcomes Study 36 Item Short-Form Health Survey (SF-36) physical and mental health components and the Chronic Respiratory Questionnaire (CRQ) [11,22].

## 2. Materials and methods

### 2.1. Subjects

This study is an analysis of baseline data collected as part of an observational cohort study of 302 participants with moderate to very severe COPD enrolled at both University hospitals and VA health care systems in San Antonio, Texas and Seattle, Washington. Study inclusion criteria included a  $FEV_1/FVC$  ratio  $<0.70$  with a  $FEV_1$  percent predicted  $<80\%$ , age  $\geq 40$  years, having smoked ten or more pack-years of cigarettes, and English speaking. Patients were excluded if they had any of the following: other types of lung disease, non-COPD-related chronic inflammatory diseases (e.g. chronic antibiotic use, ongoing infection, or auto-immune disease), lung or metastatic cancer, severe chronic kidney disease, uncompensated heart failure, advanced liver disease, HIV/AIDS, chronic oral prednisone use, bipolar disease, psychotic disorders, and dementia. Three hundred and one participants had baseline data on both parts of the TMT, of whom 198 also had baseline MIS scores; all individuals with baseline cognitive data were included in the analysis. This study was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01074515) and approved by the respective institutional review boards at three clinical sites: University of Washington, Seattle (37332), VA Puget Sound Health Care System (00240), and University of Texas Health Science Center at San Antonio/South Texas Veterans Health Care System (HSC20100373H).

### 2.2. Study design

All patients completed a baseline study visit including

spirometry, cognitive screens, a set of questionnaires, a standard 6-min walk, and a grip strength test. Following the baseline visit, participants were contacted via phone by a research coordinator and asked to complete standard measures of depressive and anxiety symptoms. This is a cross-sectional analysis of baseline data collected as part of this ongoing study.

### 2.3. Measures

#### 2.3.1. Cognition

The TMT-A, TMT-B, and MIS were used as primary predictor variables. The TMT-A measures psychomotor speed and visual attention, while the TMT-B measures the same processes with the addition of mental flexibility, a marker of executive control functioning. Each TMT score was then transformed into a z-score value normalized for age, gender, level of education, and race [14,15]. We then categorized the Z score values into three groups: normal (z-score  $> -1.0$ ), borderline (z-score  $-1.0$  to  $-1.5$ ), and impaired (z-score  $< -1.5$ ).

A memory assessment was not part of the original baseline visit, however the MIS [20] was added to the baseline visit after enrollment had already begun, and was therefore obtained on only 198 participants during the baseline visit. MIS scores range from zero to eight with higher scores indicating better memory. We used the cut-off value of  $\leq 6$  to define impairment.

#### 2.3.2. Physical functioning

Participants completed a 6-MWT during which the total number of feet walked in a six-minute period was recorded [23]. Total daily steps taken was measured using a StepWatch 3 activity monitor worn on the ankle. We used the mean score over a 7 day period [24]. To measure grip strength, participants were asked to squeeze a hand-held dynamometer with their dominant hand to their maximum capacity for 10–15 s. With at least 30 s in-between, participants repeated this two more times for a total of three grip tests. We used the mean score of the three grip tests to assess overall grip strength.

#### 2.3.3. Health-related quality of life

We used the Medical Outcomes Study 36 Item Short-Form Health Survey (SF-36) to assess general HRQOL [25]. We calculated the physical and mental component summary scores (PCS and MCS), which are standardized based on the general U.S. population [26]. We also used the Chronic Respiratory Questionnaire (CRQ), a validated instrument that measures COPD-specific HRQOL in four domains: mastery, emotional functioning, fatigue, and dyspnea [27].

#### 2.3.4. Covariates

We included several covariates to adjust for disease severity, comorbidity, psychological functioning, and demographic characteristics. COPD severity measures included forced expiratory volume in 1 s percent predicted ( $FEV_1\%$ ), the modified Medical Research Council (mMRC) dyspnea scale [28], COPD hospitalization in the last year (yes/no) and use of supplemental oxygen (yes/no). We also calculated a BODE index (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity) [29], a composite multidimensional COPD severity measure that includes  $FEV_1\%$ , 6MWT, mMRC dyspnea scale, and body mass index (BMI) [28]. Comorbidity was assessed with BMI and the Charlson Comorbidity Index (CCI) [30], a commonly used weighted composite measure of common chronic conditions. The Hospital Anxiety and Depression (HAD) Questionnaire [31] and the Patient Health Questionnaire (PHQ-9) [32] were used to assess emotional functioning. HADS and PHQ-9 scores were analyzed as continuous variables; supplemental analyses used a PHQ-9 cut-off value of  $\geq 10$  to denote possible major depression [32]. Demographic characteristics of the sample

included age, sex, race, living arrangements (alone/with others) and educational attainment.

#### 2.4. Statistical analysis

All statistical analyses were performed using baseline data of the study. Differences in characteristics of COPD patients grouped by TMT-A and TMT-B Z-score categories (normal, borderline, impaired) were compared using one-way analysis of variance and  $\chi^2$  tests. We estimated unadjusted and adjusted regression models with TMT-A, TMT-B, and the MIS as the main predictor variables, adjusting for COPD disease severity, comorbidities, psychological functioning, and demographic characteristics. Analyses were performed using Stata, Version 13.0 statistical software [33].

### 3. Results

We present demographic characteristics and health functioning indicators by TMT-A and TMT-B cognition status in Table 1. Across

the entire analytic sample (n = 301), 29.2% were classified as either having either borderline or impaired performance on measures of simple psychomotor speed (TMT-A) and executive control functioning (TMT-B). Among the 198 (66%) participants who completed the MIS, 15.7% had significant memory impairment. In bivariate analysis, slower psychomotor speed was associated with shorter distance on the 6-MWT (TMT-A:  $P = 0.03$ ) and both slower psychomotor speed and poor executive control functioning were associated with lower grip strength (TMT-A:  $P = 0.002$ ; TMT-B:  $P = 0.02$ ). Neither psychomotor speed nor executive control functioning were associated with total steps per day. Slower psychomotor speed was associated with lower scores on the SF-36 mental component summary score (TMT-A:  $P = 0.005$ ). In the subgroup of participants who completed the MIS, slower psychomotor speed was associated with memory impairment (TMT-A:  $P = 0.001$ ). There were no associations between any measures of cognitive function and either depression or anxiety.

Poorer cognitive performance, as measured by the TMT-A and TMT-B, was associated with greater disease severity as measured

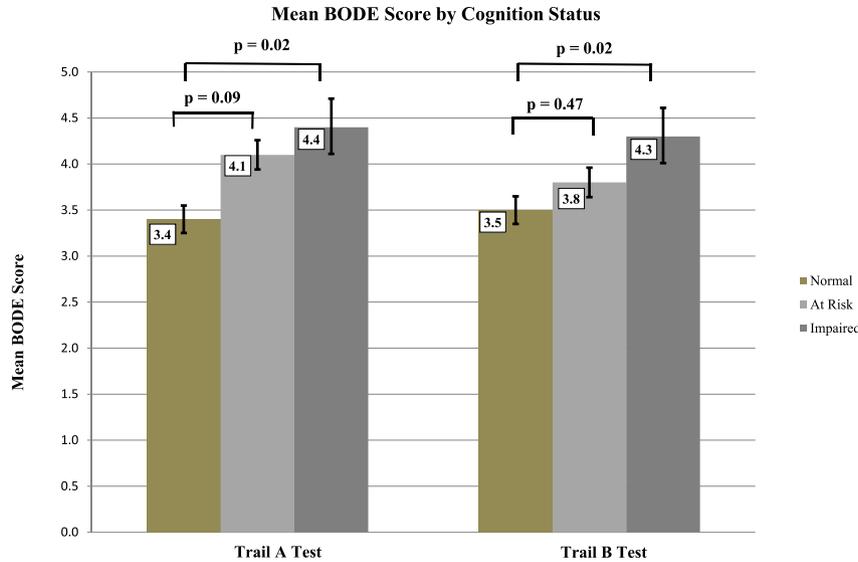
**Table 1**  
Sample demographic and health characteristics by normal, at risk, and impaired cognition status (n = 301).

Characteristics	TMT-A <sup>a</sup>			P value	TMT-B <sup>a</sup>			P value
	Normal (n = 213)	Borderline (n = 44)	Impaired (n = 44)		Normal (n = 213)	Borderline (n = 38)	Impaired (n = 50)	
<b>Demographics</b>								
Age, mean (SD), y	67.1 (8.5)	68.5 (8.1)	69.3 (9.4)	0.23	67.2 (8.8)	69.3 (8.5)	68.3 (7.4)	0.32
Male sex, No. (%)	175 (82.2)	33 (75.0)	34 (77.3)	0.47	172 (80.8)	33 (86.8)	37 (74.0)	0.31
White, No. (%)	188 (88.3)	37 (84.1)	38 (86.4)	0.73	189 (88.7)	32 (84.2)	42 (84.0)	0.54
Education, No. (%)								
High School or less	52 (24.4)	7 (15.9)	9 (20.5)	0.44	50 (23.5)	6 (15.8)	12 (24.0)	0.87
Some higher education	111 (52.1)	21 (47.7)	23 (52.3)		108 (50.7)	21 (55.3)	26 (52.0)	
College graduate	50 (23.5)	16 (36.4)	12 (27.3)		55 (25.8)	11 (28.9)	12 (24.0)	
Lives alone, No. (%)	58 (27.2)	12 (27.3)	9 (20.5)	0.64	56 (26.3)	8 (21.1)	15 (30.0)	0.64
MIS <sup>b</sup> , No. (%)								
Normal	127 (88.8)	24 (85.7)	16 (59.3)	0.001	124 (87.3)	21 (80.8)	22 (73.3)	0.13
Impaired	16 (11.2)	4 (14.3)	11 (40.7)		18 (12.7)	5 (19.2)	8 (26.7)	
Body Mass Index, mean (SD)	28.4 (6.2)	27.8 (5.9)	27.0 (5.8)	0.35	28.2 (6.2)	27.4 (6.5)	28.5 (5.4)	0.70
COPD Disease Severity, mean (SD)								
BODE Index	3.4 (2.2)	4.1 (2.5)	4.4 (2.3)	0.02	3.5 (2.2)	3.8 (2.2)	4.3 (2.6)	0.07
FEV1, % Predicted	45.5 (16.2)	43.5 (15.5)	43.9 (14.4)	0.66	45.5 (16.0)	45.6 (16.0)	42.3 (15.3)	0.43
mMRC Dyspnea Scale	1.8 (1.1)	2.2 (1.1)	2.1 (1.2)	0.07	1.8 (1.1)	2.0 (1.1)	2.2 (1.2)	0.05
Home oxygen use, No. (%)	64 (30.1)	18 (40.9)	18 (40.9)	0.19	70 (32.9)	12 (31.6)	18 (36.0)	0.89
COPD Hospitalization in past year, No. (%)	24 (11.3)	9 (20.5)	7 (15.9)	0.23	25 (11.7)	3 (7.9)	12 (24.0)	0.06
Charlson Comorbidity Index, mean (SD)	0.9 (1.1)	0.8 (1.3)	1.2 (1.5)	0.26	1.0 (1.2)	0.8 (1.2)	0.9 (1.1)	0.74
Characteristics	Normal (n = 213)	Borderline (n = 44)	Impaired (n = 44)	P value	Normal (n = 213)	Borderline (n = 44)	Impaired (n = 44)	P value
<b>Functional Status</b>								
6-Minute Walk Test, mean (SD), ft.	1122 (375)	1025 (328)	976 (377)	0.03	1113.3 (361.2)	1065.4 (346.9)	987.7 (421.1)	0.09
Total Steps per day, mean (SD)	6216 (3417)	5391 (3045)	5575 (3220)	0.24	6071 (3217)	6439 (3689)	5368 (3563)	0.30
Grip strength, mean (SD), kg.	33.6 (9.4)	29.1 (8.9)	29.4 (9.8)	0.002	33.3 (9.8)	30.2 (7.6)	29.6 (9.2)	0.02
<b>Health-Related Quality of Life CRQ, mean (SD)</b>								
Global score	4.7 (1.1)	4.5 (1.2)	4.4 (1.1)	0.08	4.7 (1.1)	4.6 (1.1)	4.5 (1.1)	0.49
Mastery	5.2 (1.4)	4.9 (1.5)	4.9 (1.3)	0.21	5.2 (1.4)	5.0 (1.4)	4.9 (1.4)	0.48
Emotional functioning	4.8 (1.2)	4.6 (1.3)	4.4 (1.3)	0.12	4.8 (1.2)	4.6 (1.3)	4.5 (1.3)	0.38
Fatigue	4.0 (1.2)	3.8 (1.3)	3.8 (1.3)	0.22	4.0 (1.2)	4.1 (1.2)	3.9 (1.3)	0.73
Dyspnea	4.9 (1.4)	4.5 (1.3)	4.5 (1.5)	0.12	4.8 (1.4)	4.8 (1.4)	4.6 (1.4)	0.64
<b>SF-36 Health Survey, mean (SD)</b>								
PCS	34.7 (9.6)	33.1 (9.0)	33.1 (10.2)	0.40	34.2 (9.5)	35.4 (10.3)	33.5 (9.3)	0.65
MCS	48.1 (8.7)	46.0 (9.1)	43.4 (10.4)	0.005	47.5 (8.9)	46.9 (9.0)	45.8 (10.4)	0.51
<b>Psychological Functioning, mean (SD)</b>								
HADS depression	3.9 (4.0)	4.8 (4.5)	5.0 (4.1)	0.17	4.0 (4.1)	4.4 (4.0)	4.8 (4.1)	0.42
HADS depression (Score $\geq 8$ ), No. (%)	43 (20.2)	12 (27.3)	14 (31.8)	0.19	47 (22.1)	9 (23.7)	13 (26.0)	0.83
HADS anxiety	4.8 (3.8)	5.2 (3.7)	5.8 (4.5)	0.33	5.0 (4.0)	4.3 (3.7)	5.5 (3.7)	0.39
HADS anxiety (Score $\geq 8$ ), No. (%)	49 (23.0)	12 (27.3)	15 (34.1)	0.29	51 (23.9)	9 (23.7)	16 (32.0)	0.49
PHQ-9 (Score $\geq 10$ ), No. (%)	41 (19.3)	12 (27.3)	12 (27.3)	0.31	45 (21.1)	8 (21.0)	12 (24.0)	0.90

TMT = Trail Making Test; BODE = Body mass index, airflow Obstruction, Dyspnea and Exercise capacity; FEV = Forced Expiratory Volume; mMRC = modified Medical Research Council; CRQ = Chronic Respiratory Questionnaire; MIS = Memory Impairment Screen; HADS = Hospital Anxiety and Depression Scale; PHQ-9 = Patient Health Questionnaire Depression; PCS = Physical Component Summary Score; MCS = Mental Component Summary Score; SD = Standard Deviation.

<sup>a</sup> Based on Z Scores.

<sup>b</sup> N = 198 due to missing data on the MIS measure.



Note: p values denote statistical significance from the baseline category "normal"; BODE = Body mass index, airflow Obstruction, Dyspnea and Exercise capacity

Fig. 1. Mean BODE (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity) Index scores by Cognition status for Trail Making Tests A and B.

with the BODE index and the mMRC dyspnea scale but not FEV<sub>1</sub>%, home oxygen use, or COPD hospitalizations in the last year (see Table 1 and Fig. 1). Specifically, we found higher mean scores on the BODE among those with slower psychomotor speed (TMT-A: Impaired Mean = 4.4; Normal Mean = 3.4,  $P = 0.02$ ) and among those with poor executive control functioning (TMT-B: Impaired Mean = 4.3; Normal Mean = 3.5,  $P = 0.02$ ). Higher mean scores of the

mMRC Dyspnea Scale were observed among those with slower psychomotor speed (TMT-A: Impaired Mean = 2.1; Normal Mean = 1.8,  $P = 0.10$ ) and among those with poor executive control functioning (TMT-B: Impaired Mean = 2.2; Normal Mean = 1.8;  $P = 0.02$ ).

We present the unadjusted and adjusted associations of Trails A and B z-score categories with each of the outcome variables in Table 2. Unadjusted analyses showed that cognitive impairment

Table 2  
Unadjusted and adjusted<sup>a</sup> associations of TMT-A and TMT-B with physical functioning and quality of life (n = 301).

Outcome variables	TMT-A		TMT-B	
	$\beta$ Unadjusted (95% CI)	$\beta$ Adjusted (95% CI)	$\beta$ Unadjusted (95% CI)	$\beta$ Adjusted (95% CI)
6-MWT				
Borderline <sup>b</sup>	-97.1 (-217.2, 23.0)	-37.6 (-140.8, 65.6)	-48.0 (-176.2, 80.3)	-39.4 (-149.0, 70.2)
Impaired	-146.2 (-266.3, -26.1)*	-95.4 (-199.2, 8.4)	-125.6 (-240.0, -11.2)*	-59.3 (-158.2, 39.5)
Total Steps/day				
Borderline	-824.7 (-1939.8, 290.4)	-297.1 (-1277.3, 683.1)	367.7 (-810.0, 1545.3)	514.5 (-509.3, 1538.3)
Impaired	-640.8 (-1778.7, 497.2)	-317.6 (-1319.0, 683.9)	-702.8 (-1769.7, 364.1)	-80.6 (-1020.3, 859.0)
Grip Strength				
Borderline	-4.4 (-7.5, -1.4)**	-2.9 (-5.5, -0.4)*	-3.0 (-6.3, 0.2)	-3.0 (-5.7, -0.3)*
Impaired	-4.2 (-7.2, -1.1)**	-2.2 (-4.8, 0.3) <sup>†</sup>	-3.7 (-6.6, -0.7)*	-2.5 (-4.9, -0.0)*
SF-36 PCS				
Borderline	-1.6 (-4.8, 1.5)	-0.1 (-2.8, 2.6)	1.1 (-2.2, 4.5)	1.3 (-1.5, 4.1)
Impaired	-1.7 (-4.8, 1.5)	-0.3 (-3.0, 2.4)	-0.8 (-3.7, 2.2)	1.2 (-1.3, 3.7)
SF-36 MCS				
Borderline	-2.1 (-5.1, 0.8)	-2.1 (-4.9, 0.7)	-0.6 (-3.8, 2.5)	-1.3 (-4.3, 1.7)
Impaired	-4.8 (-7.7, -1.8)**	-4.7 (-7.5, -1.8)**	-1.7 (-4.5, 1.2)	-1.8 (-4.5, 0.9)
CRQ Mastery				
Borderline	-0.3 (-0.7, 0.2)	-0.1 (-0.6, 0.3)	-0.2 (-0.7, 0.3)	-0.2 (-0.6, 0.2)
Impaired	-0.3 (-0.8, 0.1)	-0.2 (-0.6, 0.3)	-0.2 (-0.7, 0.2)	-0.1 (-0.5, 0.3)
CRQ EF				
Borderline	-0.2 (-0.6, 0.2)	-0.2 (-0.5, 0.2)	-0.1 (-0.6, 0.3)	-0.2 (-0.6, 0.2)
Impaired	-0.4 (-0.8, 0.0)	-0.3 (-0.7, 0.0)	-0.3 (-0.7, 0.1)	-0.2 (-0.6, 0.1)
CRQ Fatigue				
Borderline	-0.3 (-0.7, 0.1)	-0.2 (-0.5, 0.2)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.5)
Impaired	-0.3 (-0.7, 0.1)	-0.2 (-0.6, 0.2)	-0.1 (-0.5, 0.3)	0.0 (-0.3, 0.4)
CRQ Dyspnea				
Borderline	-0.4 (-0.8, -0.1)	-0.1 (-0.4, 0.3)	-0.1 (-0.5, 0.4)	-0.1 (-0.4, 0.3)
Impaired	-0.4 (-0.8, 0.1)	-0.1 (-0.5, 0.2)	-0.2 (-0.6, 0.2)	0.1 (-0.2, 0.4)

TMT = Trail Making Test; 6MWT = 6-Minute Walk Test; CRQ = Chronic Respiratory Questionnaire; PCS = Physical Health Component Summary Scale; MCS = Mental Health Component Summary Scale, EF = Emotional Functioning.

<sup>†</sup> $P < 0.10$ , \* $P < 0.05$ , \*\* $P < 0.01$ .

<sup>a</sup> Adjusted for age, sex, living arrangements, FEV<sub>1</sub> predicted, home oxygen use, MRC Dyspnea, hospitalization in past year, body mass index, and the Charlson Comorbidity Index.

<sup>b</sup> Reference category is Normal.

was significantly associated with shorter distance walked during the 6-MWT (146.2 feet,  $P < 0.05$  and 125.6 feet,  $P < 0.05$ , respectively) compared to those classified as normal. After adjustment for disease severity and other variables, however, cognitive impairment on the TMT-A and TMT-B was no longer associated with decreased 6-MWT. Both TMT-A and TMT-B showed significant unadjusted and adjusted associations with grip strength. Specifically, adjusted analyses showed decreased grip strength in those with borderline ( $P < 0.05$ ) and impaired ( $P < 0.10$ ) TMT-A performance as well as borderline ( $P < 0.05$ ) and impaired ( $P < 0.05$ ) TMT-B performance.

For the SF-36 summary scores, in both the unadjusted and adjusted analyses, only participants with cognitive impairment based on the TMT-A had lower MCS scores ( $P < 0.01$ ). No significant associations were observed between the TMT-B and SF-36 MCS. Similarly, no significant associations were observed between the TMT-A and the TMT-B with the SF-36 PCS. After adjustment, none of the four CRQ domains were significantly associated with the TMT-A or TMT-B; only the impaired TMT-A was marginally significantly associated with CRQ emotional functioning. Unadjusted and adjusted analyses of the MIS with outcome measures indicated only one significant association, with the SF-36 MCS ( $B = -3.6$ ;  $P < 0.05$ ), and marginally significant associations with the CRQ-Emotion and CRQ-Dyspnea sub-scales (see Table 3).

#### 4. Discussion

The goal of this study was to better understand the relationship of cognitive functioning (psychomotor speed, executive control functioning, and memory) with physical functioning and HRQL among COPD patients. In doing so, it is worth noting that nearly 30% of our sample were classified as having either borderline or impaired cognitive functioning on tests measuring psychomotor speed and executive control functioning. We found that although psychomotor speed (TMT-A) was associated with 6-MWT, grip strength, SF-36 MCS score, and COPD-specific QOL measures in unadjusted analyses, after adjustment for disease severity most of these relationships were no longer significant. Only grip strength was still associated with both psychomotor speed (TMT-A) and executive control functioning (TMT-B) scores in adjusted analyses, whereas SF-36 MCS scores were associated with psychomotor speed only in adjusted analyses.

Our results, demonstrating robust associations of indicators of cognitive impairment on TMTs with grip strength independent of

disease severity, comorbidity, and demographic characteristics support growing evidence of the relationship between cognitive impairment and indicators of physical infirmity among those with severe morbidities [34]. Prior studies in older adults have found that global cognitive impairment is associated with weak handgrip strength. Specifically, one analysis showed that cognitive impairment predicted significant declines in handgrip strength over a seven-year follow-up, with handgrip strength playing a mediating role between cognitive declines and disability [35]. A second study with the same sample demonstrated that decreased handgrip strength at baseline predicted significant future declines in cognitive functioning [36].

Our finding that cognitive status was not significantly associated with the 6MWT independent of COPD disease severity may suggest, as others have shown, that loss of muscle strength precedes the decline in walking speed during the evolution of physical infirmity [37], and that cognitive status, like handgrip strength, may reflect a general reduction of physiological vitality and resilience [38,39]. For example, one prospective cohort study of non-institutionalized older adults showed significant declines in lower body physical functioning and increased risk of mortality at six-year follow-up for persons with worse performance on the Trail Making Tests at baseline [40]. A future aim of our study is to make similar longitudinal assessments of cognitive status effects in our cohort of COPD patients. More longitudinal research is warranted to better understand the processes by which cognitive status and physical functioning status interact to predict disease progression and disability among COPD patients and whether interventions focused on improving cognition would alter outcomes.

In regards to HRQL, the only significant associations we found were between psychomotor speed (TMT-A) and memory impairment (MIS) and overall mental wellbeing as measured by the SF-36 MCS summary score. Interestingly, specific measures of anxiety and depression were not associated with cognitive performance. One prior study among COPD patients has found significant associations between both the physical and mental health components of the SF-36 and each of the Trail Making Test components; however, TMT scores were not standardized for age, gender, education or race, perhaps explaining the difference in the results [41]. The lack of association of cognitive functioning with either anxiety or depression may be accounted for by our choice of cognitive measures that index specific, rather than global, cognitive abilities and, at least for trail making tests, normalized values. However, we could not assess the predictive longitudinal effect of one on the other; one longitudinal study found that the onset of depression was predictive of cognitive decline among COPD patients [42].

Given the important influence of age and education on TMT-A and TMT-B scores, standardizing data by converting the time needed to complete each test to a z-score for classification of cognitive function is important to distinguish disease-related factors from demographic effects [14,15]. Patients with COPD tend to be older, and often with lower educational status. For example, in our sample, the mean age was 67.6 and nearly one quarter either did not complete high school or had only a high school diploma. In addition, identifying groups of patients with borderline cognitive impairment based on z-scores is more relevant clinically than an unadjusted time on the TMT.

Our null findings of cognitive impairment associations with the CRQ domains after adjustment for disease severity supports similar findings from another study among COPD patients [1]. We found markers of disease severity to be more predictive of HRQL than cognitive status. The abundance of null findings with the MIS suggest that memory impairment is both less frequent and less important than deficits in psychomotor speed and executive control functioning for predicting physical functioning and health-

**Table 3**  
Unadjusted and adjusted<sup>a</sup> associations of an abnormal Memory Impairment Screen with selected outcomes (n = 198).

Outcome variables	Memory impairment screen (1 = impaired memory)	
	$\beta$ Unadjusted (95% CI)	$\beta$ Adjusted (95% CI)
6-MWT	-28.2 (-163.3, 106.9)	7.8 (-102.5, 118.1)
Total Steps/day	-38.1 (-1363.1, 1286.8)	410.7 (-712.5, 1534.0)
Grip Strength	-1.4 (-5.1, 2.3)	-0.0 (-3.1, 3.1)
SF-36 PCS	1.2 (-2.4, 4.9)	1.1 (-2.2, 4.3)
SF-36 MCS	-3.2 (-6.8, 0.3)	-3.6 (-7.0, -0.1)*
CRQ Mastery	-0.2 (-0.8, 0.3)	-0.2 (-0.7, 0.3)
CRQ Emotion	-0.3 (-0.8, 0.2) <sup>‡</sup>	-0.4 (-0.8, 0.0) <sup>‡</sup>
CRQ Fatigue	0.1 (-0.4, 0.6)	0.0 (-0.4, 0.5)
CRQ Dyspnea	-0.3 (-0.8, 0.2) <sup>‡</sup>	-0.4 (-0.8, 0.0) <sup>‡</sup>

MWT = Minute Walk Test; CRQ = Chronic Respiratory Questionnaire; PHC = Physical Health Component; MHC = Mental Health Component.

<sup>‡</sup> $P < 0.10$ , \* $P < 0.05$ .

<sup>a</sup> Adjusted for age, sex, living arrangements, FEV1% predicted, home oxygen use, MRC Dyspnea, hospitalization in past year, body mass index, and the Charlson Comorbidity Index.

related quality of life in COPD.

There are clinical implications of our findings. First, we found that borderline or impaired performance on tests of simple psychomotor speed and executive control functioning is present in a subgroup of individuals with moderate to severe COPD with few comorbid conditions, and is associated with some indicators of physical functioning and health-related quality of life. Impaired memory (MIS) was less common and less consequential in this group of patients. Second, signs of cognitive impairment may be an early indicator of emerging overall physical debility among COPD patients. Both cognitive impairment and physical debility have been shown to increase the risk of hospitalization, disability, and death [9,43,44]. Third, while the evidence is limited among COPD patient population [45], impaired cognition may place COPD patients at risk for mismanaging medications [46] and other self-care behaviors essential to optimal disease management. Therefore, upon a positive screen for cognitive impairment, case management teams may want to initiate evidence-based interventions that help prevent accidents and injury associated with cognitive impairment and increased frailty, and identify ways to support effective disease self-management behaviors in patients with impaired executive functioning.

Some study limitations are worth noting given our findings. Our sample was limited to “healthier” COPD patients since we excluded patients having comorbidities with known underlying inflammation, and thus may have limited application to the general COPD population. This analysis used only baseline data and thus we cannot draw conclusions of causality that longitudinal assessments can. Although we used validated cognitive screening tests, they do not measure all aspects of cognitive functioning. We measured exercise capacity with the 6-MWT, which is commonly used in COPD, and has good concurrent validity compared to conventional exercise testing [47]. However, it is possible that cognitive function may be related to maximal exercise capacity as measured with an incremental exercise test.

We used a number of measures, including oxygen use as an index of chronic hypoxemia, to control for the potential confounding effects of disease severity. However, self-reported oxygen use is an indirect and inexact measure of the total extent of hypoxemia or fluctuations across time, which have not been studied as potential contributors to impaired brain function. With respect to TMT-A and TMT-B, the baseline cross-sectional analyses we report cannot provide information about the stability of the cognitive classifications we chose or whether individuals with borderline cognitive impairment are more likely than those with normal cognition to worsen over time. Nevertheless, we believe that use of cognitive screening tools that are practical in routine clinical care (TMTs and MIS) with standardization of values to reduce demographic influences on test performance adds significantly to the understanding of the contribution of cognitive impairment to the impact of COPD in patients.

## 5. Conclusion

We found that borderline and impaired cognitive functioning measured with the Trail Making Tests are common in COPD and associated with disease severity. Most relationships with other measures of physical function and disease specific quality of life found in unadjusted analyses were no longer significant after adjustment for COPD disease severity. In adjusted models, TMT performance was associated with handgrip strength and the MCS score of the SF-36. This suggests that specific domains of cognitive impairment are associated with COPD patients' risk of frailty and poor overall mental functioning. Notably, memory was less likely to be impaired in COPD and less strongly associated with measures of

disease severity than was psychomotor speed and executive control functioning. Further research is needed to better understand the effect of cognitive impairment on COPD outcomes, and whether it might be a suitable target for interventions to improve clinical outcomes in COPD.

## Conflict of interest

None of the authors have a conflict of interest.

## Funding

This grant was funded by grant R01HL093146 from the National Heart, Lung, and Blood Institute (NHLBI). The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the VA.

## Acknowledgements

Mark Schure completed the study analyses and contributed to the manuscript development and, as lead author, takes primary responsibility for the integrity of the work. Soo Borson, Huong Nguyen, Emily Trittschuh, Stephen Thielke, and Vincent Fan provided content expertise and contributed to the manuscript development. Kenneth Pike provided statistical expertise, conducted and confirmed final analyses, and contributed to the manuscript development. Sandra Adams assisted with data quality and preparation and contributed to the manuscript development. This grant was funded by grant R01HL093146 from the National Heart, Lung, and Blood Institute (NHLBI). Dr. Schure's work is supported by VA Postdoctoral Fellowship TPP 61-028.

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