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Impact of cognitive capacity on physical performance in chronic obstructive pulmonary disease patients: A scoping review

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is often accompanied by impaired cognitive and physical function. However, the role of cognitive function on motor control and purposeful movement is not well studied. The aim of the review was to determine the impact of cognition on physical performance in COPD. **Methods:** Scoping review methods were performed including searches of the databases: MEDLINE, EMBASE, Cochrane Systematic Reviews, Cochrane (CENTRAL), APA PsycINFO, and CINAHL. Two reviewers independently assessed articles for inclusion, data abstraction, and quality assessment. **Results:** Of 11,252 identified articles, 44 met the inclusion criteria. The review included 5743 individuals with COPD (68% male) with the forced expiratory volume in one second range of 24–69% predicted. Cognitive scores correlated with strength, balance, and hand dexterity, while 6-min walk distance (n = 9) was usually similar among COPD patients with and without cognitive impairment. In 2 reports, regression analyses showed that delayed recall and the trail making test were associated with balance and handgrip strength, respectively. Dual task studies (n = 5) reported impaired balance or gait in COPD patients compared to healthy adults. Cognitive or physical Interventions (n = 20) showed variable improvements in cognition and exercise capacity. **Conclusions:** Cognition in COPD appears to be more related to balance, hand, and dual task function, than exercise capacity.

Keywords

Cognition, exercise, lung disease, obstructive, dual tasking, pulmonary rehabilitation

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction.[1] In 2019, COPD had an estimated global prevalence of 391 million[2] and was the third leading cause of death worldwide.[3] The clinical features of airflow limitation, lung hyperinflation, respiratory muscle weakness, and dyspnea, contribute to the exercise intolerance often present in COPD.[4] Exercise capacity as measured by the 6-min walk test (6MWT)[5,6] and the level of physical activity[7] are predictors of mortality in COPD patients.

Along with the respiratory manifestations described, COPD is a systemic disease that is often accompanied by extrapulmonary sequela including cognitive dysfunction.[8] The reported prevalence of cognitive impairment in COPD patients is variable ranging between 10 to 61%,[9] and as high as 77% in hypoxemic populations.[10] Moreover, impairment ranges from mild to severe cognitive impairment and dementia, as well as deficits in both global and specific cognitive domains.[11–13] Regarding specific cognitive domains, two systematic reviews both corroborate the frequent prevalence of memory and attention-related deficits in COPD.[13,14]

Related to diminished cognitive performance is dual tasking, an experimental paradigm used to evaluate decrements in cognition when an individual is required to perform a cognitive and motor task simultaneously. Dual task interference arises when there is reduced performance in either task relative to their single task equivalent.[15] There are several cognitive theories postulated to explain the reduced performance observed relative to single tasks.[16] One of the theories, the central capacity sharing model, posits that internal processing of the concurrent events is capacity-limited due to the requirements of parallel processing.[17,18] Importantly, processing speed is correlated with broad cognitive measures, such as fluid intelligence.[19] Thus, a systematic review evaluating older adults with mild cognitive impairment (MCI) observed greater dual task interference during walking relative to healthy controls.[20] Furthermore, individuals with MCI display worse postural, gait, and fine motor control relative to their non-MCI counterparts.[21]

Given the heightened prevalence of cognitive decline in COPD, and the apparent relationship of MCI and worsened dual task performance and motor control in non-COPD, it is pertinent to evaluate how cognitive capacity influences motor control in COPD patients. Additionally, as COPD patients almost invariantly exhibit dyspnea,[22] it is critical to include dyspnea within our conceptual definition of physical performance. Indeed, dyspnea is not only a physical symptom but also an interoceptive stimuli that requires cortical and subcortical processing.[23,24] In COPD, hypoxemia may lead to cognitive dysfunction through neuronal injury.[25] The aim of this scoping review was to investigate the relationship between cognitive function and motor control in COPD patients, and whether treatments improve cognitive and physical function. As cortical control is necessary for purposeful movement,[26] we hypothesize that COPD patients that exhibit cognitive impairments will have more impaired motor control compared to those without cognitive impairments.

Methods

Protocol

The draft protocol and finalized review utilize the established scoping review framework set by Arksey and O'Malley and their updated enhancements.[27–29] The draft protocol was registered prospectively with Open Science Framework on 6 September 2021 (https://osf.io/ng765/). Draft revisions were conducted after consultation and feedback from the review team.

Identifying the research question

The primary objective addressed by this scoping review was to examine how cognitive capacity influences physical performance in COPD patients. The following subquestions were addressed: 1) what is the relationship between cognitive test measures and physical performance; 2) did physical performance indicators differ when COPD patients were stratified by cognitive test scores; 3) does dual tasking influence physical performance in COPD relative to healthy adults; and 4) does baseline cognition influence cognitive and physical changes with interventions?

Information sources and search strategy

The search strategy was developed by a research librarian (AO-C) with the following key concepts: COPD, cognition, and exercise capacity. The search was executed on 20 July 2021, and a second search on 14 February 2022, in the databases: Ovid MEDLINE; Ovid Embase; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials (CENTRAL); APA PsycINFO; CINAHL complete (EBSCOhost). Conference and book materials were removed from Embase. The reference lists of retrieved publications were also examined. The searches were not limited to study design and year but were limited to humans, adults, and English language. Please see the Supplementary Appendix for the comprehensive search strategy.

Eligibility criteria

The following studies were included if they examined COPD patients of any severity: 1) by evaluating the relationship between their cognition and physical performance; 2) compared their physical performance according to stratification of their cognitive test scores; 3) examined dual task paradigms; 4) assessed cognition and physical outcomes after an intervention; and 5) evaluated the relationship between baseline cognition with physical changes with an intervention. Exclusion criteria used: 1) regression models that had cognition as an outcome variable; 2) COPD lung transplant recipients; 3) intervention studies that did not include both cognitive and physical post-treatment scores unless inclusion criterion above was met; and 4) non-English language studies. Case series, grey literature, conference proceedings and abstracts, and dissertations were excluded.

Study selection

Search results were imported into EndNote 20 and duplicates were removed using EndNote's automation tool. Pairs of reviewers (PR, SA, EF, UM, RLFF, MK) independently screened the titles and abstracts and subsequently the selected full-text articles for inclusion. Disagreement among reviewers were resolved by a third reviewer.

Data charting process

Pairs of reviewers (PR, SA, EF, UM, RLFF, MK) independently abstracted data from the full-text articles and disagreements were resolved by a third reviewer. Data abstraction included: study design, study location, inclusion and exclusion criteria, baseline characteristics (age, sex, number of participants, COPD severity, comorbidities), study protocol, and outcome measures (correlation coefficients, hypothesis testing outcomes, beta-coefficients, dual task results, and treatment outcomes).

Quality assessment

Quality assessment was performed using a 15-item modified Downs and Black checklist[30] or the full Downs and Black[31] checklist (27-items)[31] depending on study design, the latter was used for randomized trials, randomized controlled trials (RCTs), or non-randomized controlled trials. This checklist queries study quality, external and internal validity, and power. Quality assessment was conducted by pairs of independent reviewers (PR, SA, EF, UM, MK) and disagreements were resolved by a third reviewer.

Data synthesis

Baseline characteristics and cognitive and physical assessments of reports were tabulated (Table 1). Study outcomes were synthesized into three tables: cross-sectional studies that assessed the relationship between cognitive test scores and physical measure (Table 2); dual task studies (Table 3); and interventions that evaluated cognitive and physical outcomes (Table 4).

Results

The PRISMA diagram (Figure 1) summarizes the screening results.[32] The initial and second searches yielded 10,045 and 1207 articles, respectively. The number of duplicates removed was 3619. Screening resulted in 133 full-text articles to be screened for eligibility and 44 articles met the inclusion criteria.[10,33–75] Studies were excluded due to lack of a relationship between cognition and physical outcomes (n = 84); regression models utilizing cognition as an outcome rather than an explanatory variable (n = 2); drug intervention studies that evaluated pre- and post-cognitive outcomes to assess safety (n = 2); and a study that evaluated cognitive but not physical outcomes after rehabilitation.

Of the 31 studies evaluated using the modified Downs and Black checklist (see Supplementary Appendix), quality assessment scores ranged from 43.8% to 87.5%, with a mean of 65.5%. All 31 studies scored points for: stating the study hypothesis or study aim(s); clearly delineating study outcomes; clearly describing the main findings; using appropriate statistical tests; and using valid and reliable study measures. Studies demonstrated poor external validity and internal validity (confounding) with a combined mean percentage of 14.6% and 32.3%, respectively. The 31 studies had a mean score of 74.2% for internal validity (bias), with no studies receiving points for blinding outcome measures.

Of the 13 studies evaluated using the full Downs and Black checklist, quality assessment scores ranged from 46.4% to 89.3%, with a mean of 60.7%. These studies scored high for internal validity (bias) with a mean of 83.5%. The studies demonstrated poor external validity with a mean of 12.8%. Only two of the 13 studies demonstrated sufficient statistical power.

Baseline characteristics of study participants and cognitive assessment used are summarized in Table 1. Regarding the type of cognitive assessment used in the cross-sectional and longitudinal (non-intervention) studies, three studies used a comprehensive neuropsychological testing battery, seven studies used the Mini-Mental State Examination (MMSE), four studies used the Montreal Cognitive Assessment (MoCA) test, and nine studies used a combination of the Stroop Test, Trail Making Test (TMT), Digit Symbol Substitution Test (DSST), clock-drawing test (CDT), a verbal fluency test, and word recall. For the dual task studies, one applied backwards spelling, four used backwards subtraction by threes, and one of these four also applied a verbal fluency task. Among the intervention studies, 10 utilized neuropsychological testing batteries, nine utilized either the MoCA

Table 1. Baseline characteristics and assessments.

Author (Year)	Study design	Sample (*n*)	Age	Male Female	FEV_1 (% pred)	Cognitive assessment
Correlation/Regression/Mean comparison studies						
Antonelli-Incalzi (2008)	Cross-sectional	High CF COPD (48)	—	38:10	38	Raven's progressive matrices, phonemic verbal fluency test, Corsi's block-tapping task, auditory word span, rey auditory 15-word learning test, line cancellation test, copying drawings, immediate visual memory test, sentence construction
		Mid CF COPD (49)		44:5	36	
		Low CF COPD (52)		44:8	33	
Cleutjens (2018)	Cross-sectional	CI COPD (76)	63	46:30	55	Concept shifting test, letter digit substitution test, SCWT, visual verbal learning task, shortened groninger intelligence test
		CN COPD (107)	64	51:56	54	
Cruthirds (2021)	Cross-sectional	COPD (37)	68	17:20	45	TMT-B, SCWT part 3
Dag (2016)	Cross-sectional	CI COPD (16)	65	47:5	51	MMSE
		COPD (36)	60		56	MoCA
Gore (2021)	Cross-sectional	COPD (382)	75	166:216		Immediate word recall, delayed word recall, orientation, semantic verbal fluency test
Grant (1982)	Cross-sectional	COPD (203)	65	160:43		Average impairment rating, Clinician's global neuropsychological rating
Karpman (2014)	Cross-sectional	COPD (130)	68	77:53	50	DSST
Kaygusuz (2021)	Cross-sectional	COPD (60)	57	58:2	44	MMSE
Ozyemisci-Taskiran (2015)	Retrospective cross-sectional	AECOPD (133)	69	113:20	38	MMSE
Park (2015)	Cross-sectional	COPD (593)	67	382:211	28	TMT
Park (2018)	Longitudinal; secondary analysis	COPD class 1 (109)	67	64:45	28	TMT part B
		COPD class 2 (122)	67	72:50	28	
		COPD class 3 (56)	67	32:24	29	
		COPD class 4 (20)	68	15:5	30	
Park (2020)	Cross-sectional	COPD (34)	69	14:20	44	Stroop interference
Randeep (2019)	Cross-sectional	COPD (50)	65	28:22	—	DSST, TMT, MMSE, MoCA
Roncero (2016)	Cross-sectional	CI COPD (570)	70	463:107	56	MMSE
		CN COPD (370)	66	299:71	55	
Schure (2016)	Cross-sectional	TMT-A: Normal (213)	67	175:38	46	TMT-A, TMT-B
		Borderline (44)	68	33:11	44	
		Impaired (44)	69	34:10	44	
		TMT- B: Normal (213)	67	172:41	46	
		Borderline (38)	69	33:5	46	
		Impaired (50)	68	37:13	42	
Soysal Tomruk (2015)	Cross-sectional	COPD (35)	63	31:4	38	MMSE
Tudorache (2017)	Cross-sectional	COPD (62)	68	62:0	29	MoCA
Yazar (2018)	Cross-sectional	CI COPD (16)	62	13:3	3	MMSE, CDT
		CN COPD (75)	62	73:2	45	

(continued)

Table 1. (continued)

Author (Year)	Study design	Sample (*n*)	Age	Male Female	FEV_1 (% pred)	Cognitive assessment
Yohannes (2021)	Cross-sectional	CI COPD (119) CN COPD (101)	66 65	64:55 54:47	53 47	MoCA
Summary for cross-sectional		*N* = 3962	57-75	70:30%	28-56	—
Dual task studies						
Hassan (2020)	Cross-sectional	COPD (15) Healthy (20)	71 69	9:6 9:11	52 93	Backwards spelling
Heraud (2018)	Cross-sectional	COPD (25) Healthy (20)	65 70	— —	48 112	Backwards counting by 3
Morlino (2017)	Cross-sectional	COPD (40) Healthy (28)	71 70	29:11 16:12	50 116	Backwards counting by 3
Ozsoy (2021)	Cross-sectional	COPD (35) Healthy (27)	62 61	31:4 23:4	59 —	Backwards counting by 3
Van Hove (2021)	Cross-sectional	COPD (21) Healthy (21)	64 63	14:7	41	Backwards counting by 3, verbal fluency task
Summary for dual task		*N* = 136	62-71	61:21% 18% NR	41-59	—
Intervention studies						
Abumossalam (2021)	RCT	Piracetam (low dose) (42) Piracetam (high dose) (44) Control (no placebo) (40)	58 56 62	36:6 40:4 33:7	— — —	AD8 dementia screening
Adrianopoulos (2021)	Pre-post; 3-weeks inpatient PR	CI COPD (25) CN COPD (35)	68 68	16:9 19:16	46 47	MoCA, S-MMSE, T-ICS, ACE-R, visuospatial skills, memory, orientation, attention, language/executive, fluency
Aquino (2016)	Randomized trial; 4-weeks EX	CT group (14) AT group (14)	65 69	14:0 14:0	68 69	Attentive matrices test, Raven's progressive matrices, rey-immediate recall, rey-delayed recall, verbal fluency, drawing test I and II
Bonnevie (2020)	Pre-post; 8-weeks outpatient PR	CI COPD (41) CN COPD (15)	64 59	21:20 5:10	36 39	MoCA
Cleutjens (2017)	Cross-sectional; PR	CI COPD (46) CN COPD (87)	62[a]	65:68[a]	54[a]	Visual verbal learning test, groninger intelligence test, letter digit substitution test 60 s, concept shifting test, SCWT card III
Dal Negro (2012)	Rct; 12-weeks	EAA (44) Placebo (44)	75 73	32:12 29:15	— —	MMSE
Emery (1991)	Pre-post; 1-month Outpatient PR	COPD (61)	—	34:27	—	TMT-A, TMT-B, digit symbol (WAIS-R), digit span (WAIS-R), finger tapping (halstead-reitan)
Emery (1994)	Pre-post; 1-month Outpatient PR	Older COPD (13) Mid-aged COPD (14)	69 43	10:17 (total)	— -	TMT-A, TMT-B, digit symbol (WAIS-R), digit span (WAIS-R), finger tapping (halstead-reitan)
Emery (1998)	Rct; 10-weeks PR	EXESM (30) ESM (24) Waiting list (25)	65 67 67	15:15 10:14 12:13	— — —	TMT-A, TMT-B, digit vigilance, digit symbol (WAIS-R), finger tapping (halstead-reitan), verbal fluency
Etnier (2001)	RCT; 15-months outpatient AT	AT (8) Control (7)	67 70	5:3 6:1	62 68	Culture fair intelligence test

(*continued*)

Table 1. (continued)

Author (Year)	Study design	Sample (*n*)	Age	Male Female	FEV_1 (% pred)	Cognitive assessment
Ferrari (2004)	Pre-post; 12weeks home-based PR	COPD (28)	70	20:8	55	MMSE
France (2021)	Pre-post; 6weeks PR	COPD (67)	67	37:30	31	MoCA
Kilic (2021)	Randomized trial; 12-weeks	Home PR (31)	70	27:4	58	S-MMSE
		Hospital PR (27)	68	25:2	50	
Kozora (2002)	Non-RCT; 3-weeks PR	COPD PR (30)	66	15:15	40	Digit span and digit symbol subtests (WAIS-R), digit vigilance test, TMT, logical memory, visual reproduction and paired associates subtests (WMS-R), clock drawing to command, boston naming Test-15 item, controlled oral word association test, animal naming test
		Untreated COPD (29)	67	13:16	45	
		Con (21)	65	5:16	—	
Kozora (2005)	RCT	LVRS (19)	65	14:5	25	Digit span and arithmetic subtests (WAIS-R), logical memory, verbal paired associates, and faces subtests (WMS-R), digit vigilance test, TMT, complex ideational material subtest (boston diagnostic aphasia examination), controlled oral word association test, animal naming test, boston naming Test-15 item, CDT
		Medical therapy (20)	64	18:2	24	
		Con (39)	64	33:6	—	
Lavoie (2019)	RCT; 12-weeks SMBM ± bronchodilators ± EX	SMBM + T/O + EX (76)	65	45:31	49	MoCA
		SMBM + T/O (76)	65	48:28	50	
		SMBM + T (76)	65	55:21	49	
		SMBM + placebo (76)	64	53:23	47	
Liu (2021)	RCT; 12-weeks virtual PR	Virtual PR (50)	74	40:10	39	MoCA
		Routine PR (50)	75	38:12	40	
NOTT (1980)	RCT; minimum 12-months	12-h nocturnal O_2 (102)	66	82:20	30	Halstead impairment index. Russell-neuringer average impairment index, brain age quotient
		Continuous O_2 (101)	65	78:23	30	
Rosenstein (2020)	Randomized trial; 12-weeks EX	CTHI (12)	66	3:9	60	MoCA, digit span, digit symbol, and block design subtests (WAIS), TMT, SCWT, semantic verbal fluency, letter verbal fluency, RAVLT, Rey-O complex Figure (copy)
		CTVT (12)	69	6:6	66	
		HIIT (12)	67	4:8	50	
van Beers (2021)	RCT; 12-weeks training WM + 12-weeks Mainten	WM training (33)	66	13:20	58	Cambridge neuropsychological test automated battery
		Sham WM training (31)	66	16:15	61	
Summary for interventional		—	43-75	65:35%	24-69	—

ACE-R: Addenbrooke's Cognitive Examination-Revised; AECOPD: Acute Exacerbation of COPD; AT: Aerobic Training; CDT: Clock Drawing Test; CI: cognitively impaired; CF: cognitive functioning; CN: cognitively normal; CT: Combined training (Aerobic + Resistance); CTHI: continuous training at high intensity; CTVT: continuous training at the ventilatory threshold; DSST: Digit Symbol Substitution Test; EAA: Essential Amino Acid supplementation; ESM: education and stress management; EXESM: exercise and ESM; HIIT: high-intensity interval training; LVRS: Lung Volume Reduction Surgery; Mainten: Maintenance; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; mo: month; PR: Pulmonary Rehabilitation; RAVLT: Rey Auditory Verbal Learning Test; SCWT: Stroop Color and Word Test; S-MMSE: Standardized MMSE; T-ICS: Interview for Cognitive Status; SMBM + T/O + Ex: self-management behaviour modification + tiotropium/olodaterol + exercise training; TMT: Trail Making Test; TUG: Timed Up and Go; WAIS: Wechsler Adult Intelligence Scale; WAIS-R: WAIS-Revised; WM: working memory; WMS-R: Wechsler Memory Scale-Revised.

[a]Values for total combined group (CI and CN COPD).

or MMSE, one used the Culture Fair Intelligence Test, and one used the AD8 dementia screening tool.

The relationship between cognitive test scores and physical performance are summarized in Table 2.

Cognition and exercise capacity

Inconsistent findings were reported for the relationship between 6MWD and stratification of subgroups using cognitive screening tools (MoCA or MMSE) or a comprehensive neuropsychological testing battery. Observational studies did not identify a difference in 6MWD in cognitively impaired (CI) and cognitively normal (CN) subgroups.[38,42,75] Two cross-sectional studies[62,74] identified a difference in 6MWD between CI and CN subgroups when stratified by the MMSE, with the CI group having a lower mean 6MWD. However, this relationship was negated in one report after adjusting for age and education.[62] Of note, cross-sectional studies identified significant weak-to-moderate correlations between cognitive screening tools and 6MWD,[42,66,74] while another study did not find an association between the MoCA and 6MWD.[71] When using a comprehensive neuropsychological testing battery, cross-sectional studies did not identify a difference in 6MWD between CI and CN individuals.[36,40]

Other cognitive tests used to evaluate relationships with 6MWD also showed mixed results. A longitudinal study organized patients into low or high baseline TMT part B (higher scores indicate greater impairment for TMT A and B) scores (measure of executive function) and reported varying improvements in their cognitive test scores over 3 years, with those improving having higher baseline 6MWD.[64] A cross-sectional study found differences in 6MWD when stratifying COPD patients by TMT part A scores (measure of psychomotor speed) but not according to TMT part B scores; COPD patients with impaired TMT part A had lower 6MWD than patients categorized with a normal TMT part A score.[69] Moreover, TMT part A but not TMT part B was found to have a weak inverse correlation with 6MWD.[65] Another cross-sectional study found a weak correlation between TMT and 6MWD.[66] Two cross-sectional studies found the DSST, a measure of psychomotor speed, to be weakly associated[53] and weakly correlated with 6MWD.[66] The CDT, a measure of memory, attention, and visuospatial abilities had a weak correlation with 6MWD.[74]

Regarding gait speed, in a cross-sectional study using multivariate linear regression, all covariates, which included delayed word recall, immediate word recall, measurement of orientation or executive function, were not significant.[50]

Regarding cycle ergometry, Average Impairment Rating, a global index of impairment (higher score indicates greater CI), and an independent global rating by clinicians, demonstrated a weak negative correlation with maximum work.[10] TMT part A was also reported to have a weak negative correlation with maximum work, while the relationship with TMT part B was not significant.[65]

The Stroop-Color Word Test (SCWT), a measure of executive function and cognitive flexibility, and TMT part B, were both found to have a moderate inverse correlation with leg extension force.[41]

Cognition and dyspnea

Categorizing COPD patients into CI and CN subgroups according to cognitive test scores had mixed results regarding Modified Medical Research Council (mMRC) Dyspnea scores. Higher mMRC Dyspnea scores were found in CI COPD when stratifying by MMSE[67] and TMT part B,[69] while MoCA,[35,75] a comprehensive neuropsychological testing battery,[40] and TMT part A[69] stratification showed no significant differences.

Regarding other measures of dyspnea, categorizing subgroups based on a comprehensive neuropsychological battery, one cross-sectional study did not identify a difference in their Visual Analogue Scale (VAS) dyspnea scores.[36] Categorizing patients into high or low TMT part B baseline scores with varying trajectories of cognitive improvement, did not find a significant difference between their University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ) scores[64]; with TMT part B being weakly correlated with the UCSD-SOBQ, while TMT part A was not.[65]

Cognition and balance

An investigation of postural and functional balance through center-of-pressure displacement and Berg Balance Scale (BBS), respectively, found moderate correlations with Stroop interference.[63] Multiple linear regression modelling showed associations with Stroop interference score and center-of-pressure, adjusted for other covariates (see Table 2).[63] In a younger COPD cohort (mean of 57 years), the MMSE was weakly correlated with BBS, and MMSE was associated with BBS through simple linear regression.[54] Moreover, another cross-sectional study using multivariate linear regression, found an association between delayed word recall and tandem stance time.[50]

Cognition and hand function

In COPD patients categorized by TMT part A and TMT part B scores, grip strength was significantly higher in CN individuals.[69] Additionally, through multivariable regression, borderline impaired TMT part A scores and borderline impaired and impaired TMT part B scores were independently associated with decreased grip strength

Table 2. Cross-sectional studies showing relationships between cognitive test scores and physical performance.

Author (Year)	Sample	Cognitive measure	Score	Physical measure	Score	Method	Outcomes
Andrianopoulos (2021)	CI COPD CN COPD	MoCA	≤25 ≥26	mMRC	1.4 (1.0) 1.6 (0.8)	Independent *t*-test	mMRC did not differ between groups (p > 0.05)
Antonelli-Incalzi (2008)	High CI Mid CI Low CI	NTB	Scores adjusted for age and education	6MWD (m) 6MWD % pred VAS dyspnea	293 (88) 277 (124) 254 (110) 59.3 (26.0) 60.0 (26.4) 56.4 (23.3) 5.7 (3.1) 6.0 (3.7) 6.8 (3.5)	1-Way ANOVA with scheffe post hoc test	6MWD (m and %pred did not differ among groups (p = 0.216 and p = 0.762, respectively) VAS dyspnea did not differ among groups (p = 0.279)
Bonnevie (2020)	CI COPD CN COPD	MoCA	< 26 ≥26	6MWD (steps) 6MWD (m)	148 (103–202) 191 (156–246) 377 (117) 409 (112)	Mann–Whitney *U* test; Independent *t*-test	6MWD (steps and m) are comparable between CI and CN subgroups (p = 0.08; p = 0.39)
Cleutjens (2018)	CI COPD CN COPD	NTB		mMRC 6MWD (m) 6MWD % pred	2.2 (1.0) 2.3 (1.0) 421.8 (112.2) 439.2 (111.5) 66.1 (16.7) 69.8 (16.4)	Independent *t*-test; Chi-squared test	mMRC and 6MWT are similar between CI and CN COPD patients (p = 0.53; p = 0.30; p = 0.14; p = 0.16 as listed respectively)
Cruthirds (2021)	COPD	SCWT pt 3 TMT pt B	134.7 (6.8) 80.9 (6.3)	Leg extension force/kg lean mass (N/kg)	4.9 (0.2)	Pearson's correlation	SCWT pt 3 and TMT pt B negatively correlated with leg extension force (r = −0.3671, p < 0.05; r = −0.4563, p < 0.05)
Dag (2016)	CI COPD CN COPD	MMSE MoCA	≤24 > 24 < 21 ≥21	6MWD (m)	389.4 (97.5) 441.5 (117.2)	Independent *t*-test; Pearson's correlation	6MWD not different between groups for MMSE and MoCA scores (p = 0.15, p = 0.14) but correlated with MMSE and MoCA (r = 0.29, p = 0.037, r = 0.39, p = 0.004)
Gore (2021)	COPD	DWR	3.88 (1.99)	Gait speed Tandem stance time	0.69 (0.22) 24.63 (18.5)	Multivariate linear regression (covariates: IWR, orientation, executive function)	Model 1: Covariates not associated with gait speed Model 2: DWR associated with tandem stance time (β = 1.42, 95% CI 0.10–2.74, p = 0.04)

(continued)

Table 2. (continued)

Author (Year)	Sample	Cognitive measure	Score	Physical measure	Score	Method	Outcomes
Grant (1982)	COPD	AIR CGNR	2.28 (0.78) 4.38 (1.12)	Maximum cycle ergometer work		Pearson's correlation	AIR and CGNR negatively correlated with max cycle work (r = −0.18, p = 0.03; r = −0.23, p = 0.002)
Karpman (2014)	COPD	DSST	—	6MWD (m)	410 (120)	Stepwise multivariate linear regression (covariates: Gait speed, DLCO%pred, FEV1%pred)	DSST weakly associated with 6MWD (β = 1.2, p = 0.011)
Kaygusuz (2021)	COPD (mMRC <2) COPD (mMRC ≥2)	MMSE	26.63 (2.94) 25.97 (3.36)	BBS mMRC	55.20 (1.62) 52.97 (4.50) 0.60 (0.49) 2.97 (0.76)	Spearman's correlation; Simple linear regression	MMSE correlated with BBS and mMRC (r = 0.331, p = 0.001; r = −0.446, p < 0.001) and associated with BBS (β = 0.314, SE = 0.099, 95% CI = 0.117–0.512, p = 0.002)
Park & larson (2015)	COPD	TMT pt A TMT pt B	43.1 (16.0) 99.9 (44.5)	6MWD (ft) Peak work (W) UCSD-SOBQ	1104.0 (307.7) 36.1 (21.0) 58.4 (16.6)	Pearson's correlation	TMT pt a negatively correlated with 6MWD and peak work (r = −0.09, p = 0.024; r = −0.12, p = 0.007) and positively with ucsd-sobq (r = 0.09, p = 0.028) TMT B correlated with UCSD-SOBQ (r = 0.09, p = 0.028)
Park (2018)	Class 1 Class 2 Class 3 Class 4	TMT pt B	77.0 (21.5) 88.3 (19.9) 130.7 (19.5) 185.9 (52.2)	6MWD (ft) UCSD-SOBQ	1265.4 (295.7) 1139.5 (276.1) 1123.2 (308.0) 1240.5 (229.0) 59.8 (18.5) 63.0 (19.9) 64.9 (19.1) 60.4 (19.2)	1-Way ANOVA with bonferroni correction	Class 1 had greater 6MWD than classes 2 and 3 (p = 0.01) No significant differences among classes for UCSD-SOBQ (p = 0.40)
Park (2020)	COPD	Stroop interference	61.66 (3.924)	AP mean sway velocity BBS	1.11 (0.073) 53.11 (0.55)	Pearson's correlation; Multiple linear regression (covariates: O_2 therapy, fat mass, diabetic status)	Stroop interference - Correlated with postural balance and negatively with BBS (r = 0.59, p = 0.0002; r = −0.45, p = 0.048) - Associated with CoP (β = 0.009796, SE = 0.0022, p = 0.0001)
Ozyemisci-Taskiran (2015)	CI AECOPD CN AECOPD	MMSE	< 24 ≥24 < Adjusted cutoff ≥Adjusted cutoff	6MWD (m)	146 (134) 242 (152) 240 (42–360) 252 (100.5–355)	Independent t-test; Pearson χ^2; Test (adjusted for age and education)	6MWD different among unadjusted groups (p = 0.002) but not different among adjusted groups (p = 0.389)

(continued)

Table 2. (continued)

Author (Year)	Sample	Cognitive measure	Score	Physical measure	Score	Method	Outcomes
Randeep (2019)	COPD	S-MMSE MoCA TMT DSST	23.3 (3.3) 22.2 (3.6) 223 (27) 28.4 (2.2)	6MWD (m)	392.3 (124.856)	Pearson's correlation	MMSE, MoCA, TMT, and DSST correlated with 6MWD (r = 0.41, *p* = 0.00; r = 0.30, *p* = 0.03; r = 0.33, *p* = 0.02; r = 0.34, *p* = 0.02)
Roncero (2016)	CI COPD CN COPD	MMSE	< 27 ≥27	mMRC	3.1 (0.9) 2.6 (0.9)	Independent *t*-test	CI COPD had higher mMRC scores ($p < 0.001$)
Schure (2016)	TMT A CN TMT A CB TMT A CI TMT B CN TMT B CB TMT B CI	TMT A TMT B	Z-score > −1.0 Z-score −1.0 to −1.5 Z-score < −1.5	mMRC	1.8 (1.1) 2.2 (1.1) 2.1 (1.2) 1.8 (1.1) 2.0 (1.1) 2.2 (1.2)	One-way ANOVA; Multivariable regression (covariates: Age, sex, living arrangements, FEV % pred, home oxygen use, mMRC, hospitalization in past year, BMI, charlson comorbidity Index)	mMRC and 6 MWD differed in TMT part B subgroups (*p* = 0.05 and (*p* = 0.03, respectively) Grip strength differed in both TMT a and TMT B subgroups (*p* = 0.002; *p* = 0.02); Borderline impaired TMT A showed significant association with grip strength (β = -2.9, 95% CI -5.5, −0.4, $p < 0.05$). Borderline and impaired TMT B showed significant association with grip strength (β = -3.0, 95% CI -5.7, −0.3, $p < 0.05$; β = -2.5 95% CI -2.5, −0.0, $p < 0.01$, respectively)
				6MWD (ft)	1122 (375) 1025 (328) 976 (377) 1113.3 (361.2) 1065.4 (346.9) 987.7 (421.1)		
				Grip strength (kg)	33.6 (9.4) 29.1 (8.9) 29.4 (9.8) 33.3 (9.8) 30.2 (7.6) 29.6 (9.2)		
Soysal Tomruk (2015)	Hypoxemic COPD	MMSE	23.9 (3.3)	Placement dexterity (min) Turning dexterity (min)	2.1 (0.3) 2.3 (0.3)	Pearson's correlation	MMSE negatively correlated with placement and turning dexterity (r = −0.411, *p* = 0.0015; r = 0.418, *p* = 0.013)
Tudorache (2017)	COPD	MoCA	21.50 (20–24)	6MWD (m)	360 (315–400)	Spearman's Correlation	MoCA not correlated with 6MWD (r = 0.131, NS)
Yazar (2018)	CI COPD CN COPD COPD	MMSE	≤24 > 24	6MWD (m)	285.94 (136.921) 358.89 (103.696)	Independent *t*-test; Pearson's correlation	6MWD different between groups (*p* = 0.018) but mMRC similar 6MWD correlated with MMSE and CDT (r = 0.294, *p* = 0.005; r = 0.258, *p* = 0.014) but not mMRC
		CDT	4.14 (1.3)	MMRC	2.06 (1.526) 1.53 (1.057)		

(continued)

Table 2. (continued)

Author (Year)	Sample	Cognitive measure	Score	Physical measure	Score	Method	Outcomes
Yohannes (2021)	CI COPD CN COPD	MoCA	[18,26) ≥26	6MWD	1134 (842, 1356) 1198 (983, 1420)	Independent *t*-test	6MWD and mMRC did not significantly differ among subgroups (p = 0.102; p = 0.392, respectively)
		mMRC		mMRC	3 (2, 4) 3 (1, 4)		

6MWD: 6-min walk distance; AIR: average impairment rating; AP: anteroposterior; BBS: berg balance scale; CGNR: clinician's global neuropsychologic Rating; CoP: center of pressure; DLCO: diffusing capacity for carbon monoxide; DWR: delayed word recall; IWR: immediate word recall; mMRC: modified medical research council dyspnea scale; NS: non-significant; NTB: neuropsychological testing battery; UCSD-SOBQ: The University of California, San Diego shortness of breath questionnaire; VAS: visual analogue scale.

Table 3. Dual task studies—performance of COPD patients relative to healthy controls (Con).

Author (Year)	Cognitive screening (COPD vs control)	Motor task	Single task	Between group *p*-value	Dual task	Between group *p*-value	Main outcomes
Hassan (2020)	MoCA 24.2 vs 26.1 $p = 0.032$	PPW velocity	Lower	0.005	Lower	0.025	COPD exhibited decreased gait velocity in both single and dual tasks (+ backwards spelling) compared to Con
		FPW velocity	Lower	0.001	Lower	0.035	
Heraud (2018)	No screening	Gait speed	Lower	NS	Lower	NS	COPD patients exhibit increased stride time variability during dual task (+ counting backwards by 3) compared to Con
		Stride time variability	Lower	NS	Higher	<0.001	
Morlino (2017)	MMSE 26.7 vs 28.3 $p < 0.025$	TUG test	Higher	<0.05	Higher	<0.05	COPD patients exhibit longer TUG test time for single and dual tasks (+ counting backwards by 3) compared to Con
Ozsoy (2020)	No screening	TUG test	Higher	NS	Higher	NS	COPD did not differ in the TUG test and knee extension muscle force production in single and dual tasks (+ counting backwards by 3) compared to Con
		Knee extensor force	Lower	NS	Lower	NS	
Van hove (2021)[a]	No screening	DOT	Higher	NS	Higher[b]	<0.05	COPD patients exhibit greater balance-related deficits single and dual tasks (+ counting backwards by 3 or verbal fluency task) compared to Con No correlation was found between cognitive function (verbal fluency or backwards counting) and postural control
					Higher[c]	<0.05	
		Area	Higher	<0.05	Higher	<0.05	
					Higher	<0.05	
		ML RoM	Higher	<0.05	Higher	<0.05	
					Higher	NS	
		AP RoM	Higher	NS	Higher	<0.05	
					Higher	NS	
		ML SD	Higher	<0.05	Higher	NS	
					Higher	NS	
		AP SD	Higher	NS	Higher	<0.05	
					Higher	NS	
		ML speed	Higher	<0.05	Higher	<0.05	
					Higher	<0.05	
		AP speed	Higher	<0.05	Higher	<0.05	
					Higher	<0.05	
		TMV	Higher	<0.05	Higher	<0.05	
					Higher	<0.05	

Area: area of the 95% prediction ellipse; healthy controls: Con; DOT: total displacement of sway; ML: medial-lateral; RoM: Range of motion; PPW: preferred paced walk; FPW: fast paced walk; SD: CoP standard deviation; TMV: trajectory mean velocity; TUG: timed-up-and-go test.

[a]Results from eyes closed condition only shown.

[b]Results for counting backwards dual task condition.

[c]Results for verbal fluency dual task condition.

Table 4. Interventions showing within subject changes in cognition and physical performance.

Author (Year)	Sample	Cognitive measure	Result (Δ mean (SD))	Pre-post *p*-value	Physical measure	Result	Pre-post *p*-value	NS measures[a]
Pulmonary rehabilitation								
Andrianopoulos (2021)	CI COPD	S-MMSE	0.7 (1.1)	<0.05	6MWD (m)	25 (59)	<0.05	Cognitive measures: Orientation, attention
	CN COPD		0.5 (1.2)	<0.05		46 (48)	<0.05	
		T-ICS	1.1 (1.9)	<0.05	6MWD%pred	3.6 (9.3)	NS	
			1.1 (1.7)	<0.05		7.1 (7.3)	<0.05	
		ACE-R	4.4 (4.6)	<0.05	CET 75% WRpeak (s)	140 (142)	<0.05	
			1.8 (2.9)	<0.05		117 (166)	<0.05	
		Visuospatial skills	7.5 (14.4)	<0.05				
			0.4 (12.9)	NS				
		Memory	6.0 (9.3)	<0.05				
			4.2 (5.8)	<0.05				
		Language/ executive	2.1 (5.9)	NS				
			1.9 (3.4)	<0.05				
		Fluency	8.3 (16.0)	<0.05				
			0.9 (9.5)	NS				
Bonnevie (2020)	CI COPD	MoCA	1.0	<0.01	6MST	34	<0.01	
	CN COPD			0.37		27	0.03	
					6MWD (m)	28	0.10	
						34	0.08	
Cleutjens (2017)	CI COPD				6MWD (m)	21.7 (47.2)	0.003	
	CN COPD					15.7 (57.8)	0.013	
					mMRC	−0.6 (1.3)	0.013	
						−0.4 (0.9)	<0.001	
Emery (1991) and Emery (1994)[b]	Male/ Female Middle/Old	TMT part A	−2.17/-4.02	NS	VO_2max (ml/ min)	140.7/ 67.1	<0.001	Cognitive measures: Digit span forward, digit span backward, tapping non-dominant hand
			−6.76/-8.06	<0.05		212.9/ 65.54	NS	
		TMT part B	−33.9/-40.4	<0.001	Power (W)	11.7/8.54	<0.001	
			−39.1/-55.2	<0.05		20.2/7.32	<0.05/NS	
		Digit symbol	5.62/6.61	<0.001	Laps (in 12 min)	2.05/2.43	<0.05	
			11.19/6.82	<0.05/ <0.01		3.71/1.36	<0.001/ <0.05	
		Tapping dominant hand	2.05/3.61	<0.05				
			4.98/3.1	NS				

(continued)

Table 4. (continued)

Author (Year)	Sample	Cognitive measure	Result (Δ mean (SD))	Pre-post *p*-value	Physical measure	Result	Pre-post *p*-value	NS measures[a]
Emery (1998)	EXESM	Verbal fluency	5.3	<0.001	Work (kp-m)	11.3	<0.01	Cognitive measures: Digit vigilance, tapping dominant hand, tapping non-dominant hand, TMT part A, TMT part B, digit symbol
	ESM		−0.2	NS		1.8	NS	
	WL		0.4	NS		−1.0	NS	
					VO_2max (mL/kg/min)	2.0	<0.01	
						−3.0	NS	
						−0.3	NS	
Ferrari (2004)	Home PR	MMSE			Max work (W)	↑	<0.05	
					VO_2max	↑	<0.05	
France (2021)	COPD	MoCA	0.6 (2.8)	NS	SPPB	↑	<0.001	
	CI COPD		1.6 (2.4)	0.004				
	CN COPD		−0.8 (2.)	0.276				
Kilic (2021)	Home PR	S-MMSE	0.48	0.001	6MWD (m)	14.48	0.005	
	Hospital PR		0.77	0.001		68.22	<0.001	
Kozora (2002)	PR COPD	Digit vigilance	−31.3	CI 0.004	6MWD (ft)	266	<0.001	Digit span, digit symbol, TMT part B, visual retention, verbal pairs, BNT-SF, letter fluency, semantic fluency
	COPD-no PR		−17.6	NS				
			−30.7	NS		43	<0.001	
	Con	Story retention	11.1	CI 0.006				
			10.0	NS				
			9.0	NS				
		Clock score	0.4	CI 0.06				
			−0.4	NS				
			0.4	NS				

(continued)

Table 4. (continued)

Author (Year)	Sample	Cognitive measure	Result (Δ mean (SD))	Pre-post *p*-value	Physical measure	Result	Pre-post *p*-value	NS measures[a]
Liu (2021)	Virtual PR Control	MoCA	↑ ↔	<0.05	6MWD (m)	↑ ↑		
Aerobic and resistance training								
Aquino (2016)	CT AT	Attentive matrices Rey-DR Raven test Verbal fluency Drawing test II	2.43 3.15 1.35 0.64 1.72 0.64 5.0 4.0 5.71 3.21	<0.01 <0.01 <0.01 <0.05 <0.01 <0.05 <0.01 <0.01 <0.01 <0.05	VO_2max (mL/kg/min) Quadricep strength kg Arms strength kg	4.78 5.01 11.72 11.07 4.43 2.85		Cognitive measures: Rey-IR, drawing test I
Etnier (2001) 3-months exercise phase	COPD	CFIT	4.93	<0.001	6MWD (ft) VO_2max (mL/kg/min)	207 0.94	<0.001 <0.01	—
Maintenance phase(3–18 months)	Long term exercise No exercise	CFIT	2.5 −0.14	NS NS	6MWD (ft) VO_2max (mL/kg/min)	40.38 −75.85 −0.84 −1.75	NS NS <0.01 <0.01	
Rosenstein (2020) 12-weeks intervention phase	CTHI CTVT HIIT	WAIS digit span	2.4 −1.0 1.5	0.830[c] −0.310 0.423	Endurance time (s)	30.92 33.26 36.28	<0.001 <0.001 <0.001	Medium to small effect sizes during intervention phase: TMT part A, TMT part B, SCWT, semantic and letter verbal fluency, RAVLT (total 1–5), RAVLT (list B), RAVLT (immediate recall), RAVLT (delayed recall), WAIS block design, WAIS digit symbol coding

(continued)

Table 4. (continued)

Author (Year)	Sample	Cognitive measure	Result (Δ mean (SD))	Pre-post *p*-value	Physical measure	Result	Pre-post *p*-value	NS measures[a]
		Rey-O complex Figure (copy)	2.0 2.9 0	0.963 0.659 0.015				
Maintenance phase (week 12 to year 1)	CTHI CTVT HIIT	MoCA	1.7 −0.3 1.1	0.932 - -				
		SCWT (part 4-3)	−0.04 −0.58 0.49	0.111 −0.391 0.849				
Working memory (WM) training								
van Beers (2021)								Cognitive measures: Motor orientation task, paired associates learning, stop-signal task, delayed match-to-sample, spatial working memory Physical measures: 6MWD, accelerometry activity count
12-weeks intervention phase	WM training Sham training							
12-weeks maintenance phase	WM training Sham training	5-Choice movement time (RTI)	↓ ↔	0.016 0.303				

6MST: 6-min stepper test; BNT-SF: Boston Naming Test-Short Form; CET: cycle-endurance test; CFIT: Culture Fair Intelligence Test; DR: delayed recall; ESWT: endurance shuttle walk test; IR: immediate recall; MT: medical therapy; PEmax: maximal expiratory pressure; PImax: maximal inspiratory pressure; RTI: Reaction Time Task; SPPB: Short Physical Performance Battery; SNIP: sniff nasal inspiratory pressure; WL: waiting list. Some of the abbreviations are shown for Table 1.

[a]Data from the same study.

[b]Effect sizes reported instead of *p*-values.

[c]Non-significant pre-to-post measures for all study groups.

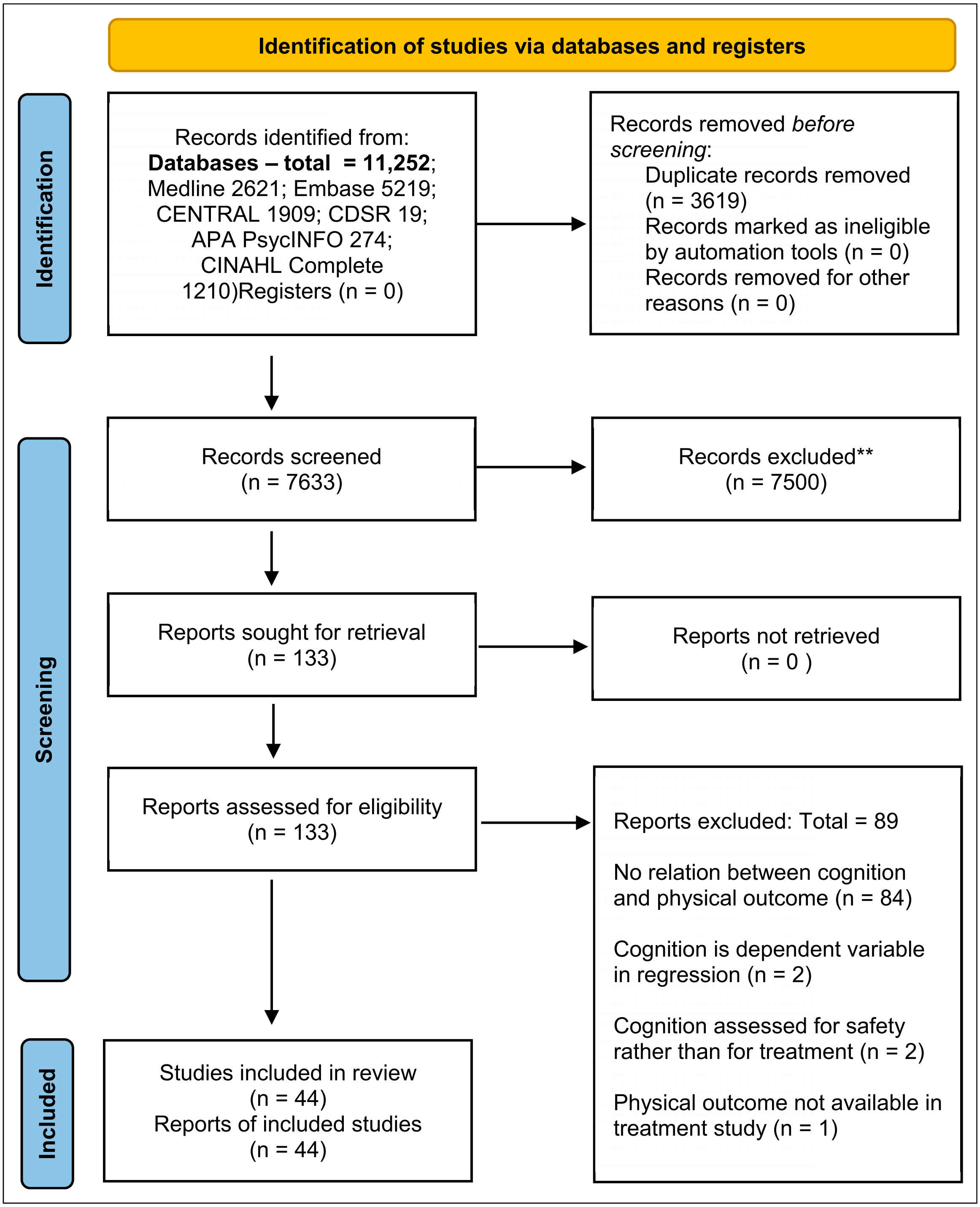

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizing search strategy results.

(Table 2).[69] Along with handgrip strength, cognition measured through MMSE had a moderate negative correlation with placement and turning dexterity in a hypoxemic cohort, with the dexterity correlation not being different in those with mild and moderate hypoxemia.[70]

Dual tasking in COPD patients compared to healthy controls

In one study, COPD patients exhibited decreased walking velocity during both single and dual task (walking and backwards spelling) conditions compared to healthy controls,[51] while another study did not report differences in gait speed in both task conditions, but did find greater stride time variability for COPD patients during dual tasking (walking and backwards counting by 3).[52] Mixed results were also found for the Timed Up and Go (TUG) test, whereby one study reported COPD patients having a longer TUG completion time in both single and dual tasks relative to healthy controls,[60] while the other did not report a difference in single and dual task conditions for the TUG test and knee extension muscle force.[61] Both studies utilized backwards counting as their cognitive task paradigm.[60,61] Regarding balance assessed through CoP displacement during dual tasking, COPD patients exhibited greater balance deficits in both single and dual tasks relative to healthy controls.[73]

Effects of interventions on cognitive outcomes in COPD patients

Pulmonary rehabilitation (PR) resulted in variable improvements among the studies assessing specific cognitive domains.[35,44–46,57] PR showed improvements in global cognition,[35,38,49,55,59] attention and processing speed,[44,45,57] executive function,[35,44–46] visuospatial skills,[35,57] and language ability.[57] Among the five PR studies showing improvements in global cognition,[35,38,49,55,59] two studies demonstrated improvements only in CI COPD patients.[38,49] All PR interventions resulted in significant improvements in physical outcomes,[35,38,39,44–46,48,49,55,57,59] with three studies[35,38,39] reporting no difference in 6MWD post-rehabilitation between CI and CN COPD patients, while investigation[38] reported CN COPD patients having significantly greater post-rehabilitation 6-min stepper test (6MST) scores than CI COPD patients. Studies evaluating whether cognition is associated with PR physical improvements showed mixed results.[38,48] Improvements in MoCA scores were not associated with changes in exercise capacity as measured by 6MWD and 6MST in hospital-based PR,[38] while baseline MMSE scores were significantly correlated with improvements in maximum cycling effort (watts) ($r = 0.46, p < 0.05$) and VO_2max ($r = 0.41, p < 0.05$) in home-based PR.[48]

Exercise interventions had variable cognitive outcomes.[37,47,68] Endurance training was shown to improve fluid intelligence,[37,47] global cognition,[68] visuospatial abilities,[37,68] working memory,[68] attention,[37] delayed recall,[37] and executive function.[37] Combined aerobic and resistance training resulted in greater improvements in delayed recall, fluid intelligence, and visuospatial abilities compared to aerobic training alone.[37]

Working memory (WM) training versus sham WM training was also studied.[72] WM refers to the short-term memory that is required to do things in the moment. Although WM span increased over 24 weeks in the intervention group, this was not reflected in improvements in cognitive test scores.[72] Moreover, physical capacity as measured by 6MWT and Short Physical Performance Battery (SPPB) showed no improvements.[72]

Other interventions such as behavioral modification,[58] lung volume reduction surgery,[56] oxygen (O_2) therapy,[33] amino acid[43] and piracetam supplementation[34] resulted in cognitive improvements. Moreover, all these therapies also improved physical outcomes except O_2 supplementation.[33,34,43,56,58]

Discussion

COPD, 6MWD, and balance

Our findings indicate that CI and CN COPD patients have comparable 6MWT scores,[36,38,42,75] with studies finding no association between cognitive impairment and 6MWD.[40,62] These findings are corroborated by the low-order correlation between global[42,74] and domain-specific[65,74] cognitive test scores and 6MWD. Similarly, dyspnea scores were comparable between CI and CN COPD patients,[35,36,40,64,74,75] with low,[65] moderate,[54] and non-significant correlations found.[74] Importantly, lower cognitive test scores were associated with impairments in balance parameters.[50,54,63]

Of clinical importance, a recent meta-analysis found that COPD patients had greater deficits in their balance compared to healthy controls.[76] Nonetheless, while shorter 6MWDs are correlated with impairments in balance function,[77–79] and a 6MWD <300 m being a predictor for balance impairments as measured by the BBS and TUG,[80] the reviewed studies indicate no difference in 6MWDs between CI and CN COPD patients. Given the importance of balance in daily activities, further exploration of interventions to improve the relationship between CI and falls are required.

Potential mechanisms underlying cognitive-physical relationship

As depicted from the results, COPD patients who display decreased cognitive capacity are more likely to exhibit impairments in balance and hand function, rather than functional exercise capacity or physical conditioning as measured by the 6MWT. Our results do not reflect a lack of relationship with 6MWD, but that the relationship with cognition and 6MWD is less pronounced. One plausible mechanism is the increased cortical sensorimotor connectivity demonstrated while standing versus walking.[81] This heightened cortical connectivity suggests greater attention is needed for balance and postural control, while walking may depend more on spinal neural networks.[81] COPD patients exhibit reduced white matter integrity and impairments in gray matter functional connectivity[82]; thus, CI COPD patients may lack the cortical resources to sustain adequate balance.

A regression model investigating cognitive-balance relationships demonstrated an association between better delayed word recall and increased tandem stance time.[50] The 10-word list used for delayed recall is often utilized to detect mild CI by assessing hippocampal and entorhinal cortical functions.[83] Poor delayed recall is associated with hippocampal[84,85] and entorhinal atrophy.[86,87] Importantly, hippocampal atrophy and its association with CI has been reported in COPD.[88] The hippocampus and entorhinal cortex receive input from the vestibular system.[89] Notably, hippocampal and entorhinal atrophy is associated with impaired vestibular function, a system important for maintaining balance.[90]

Additionally, another regression model depicted poorer TMT scores (worse executive function) associated with weaker handgrip strength.[69] The prefrontal cortex (PFC) facilitates executive function,[91] and PFC impairments can lead to worse motor planning and recruitment, and thereby reduced strength.[92,93]

Dual tasking

Similarly, cognitive-motor dual tasking induced static balance deficits in COPD patients.[73] Balance[76] and postural control[94,95] are often impaired in COPD. While several factors have been implicated in balance impairments, such as age,[96,97] dyspnea,[98] inspiratory muscle weakness,[99] and lower limb muscle strength,[98] the influence of cognition has not been investigated as thoroughly. Although, a cognitive screening test was not conducted in the dual task study by Van Hove et al.,[73] COPD patients had lower verbal fluency task scores than healthy controls.

Impairments when performing a concurrent task may arise due to processing constraints within the brain, such as the PFC. In a single-cell recording study in monkeys, dual tasking resulted in concurrent activation of the same lateral PFC region suggesting cognitive capacity limitations.[100] Related to limitations in capacity, Hassan et al.[51] observed that COPD patients did not increase dorsolateral PFC oxygenated hemoglobin (O_2Hb) from single to dual tasks, while healthy individuals did increase O_2Hb. Therefore, this observed ceiling effect in neural activity may be pivotal to the constraints in simultaneous processing. In addition to limited cognitive capacity, impairment has been reflected by reduced PFC automaticity (decrease in O_2Hb seen in tasks requiring less executive function) during single and dual task walking in COPD and older adults, respectively.[101,102]

Pulmonary Rehabilitation

In this review, the predominant intervention to facilitate cognitive-physical improvements was PR. All PR studies found significant improvements in cognition. However, of the four studies[35,38,49,57] assessing differences in PR outcomes between CI and CN COPD patients, three[38,49,57] found cognitive improvements only in CI COPD patients. Thus, the efficacy of PR cognitive improvement may also, among other factors, rely on baseline cognition.

Notably, the physical improvements that arise from PR seem to be independent from baseline cognition, as all studies specifically evaluating PR in CI COPD patients note an improvement in physical performance.[35,38,39,49] Although, Ferrari et al.[48] did find a moderate correlation between baseline MMSE scores and improvements in exercise capacity in a minimally supervised home PR setting. While compliance was assessed, potential CI may have influenced proper completion of the training sessions in a minimally supervised setting, hence the moderate correlation between MMSE scores and exercise capacity. Furthermore, Cleutjens et al.[39] found that CI COPD patients had an increased rate of PR dropout compared to CN COPD patients.

Nonetheless, despite the potential risk for PR dropouts, physical improvements were observed in CI COPD, with the 6MWT being the most frequent treatment outcome. While this scoping review identified balance as a potential factor that is impaired in CI COPD patients, most PR studies included in our review did not conduct balance assessments. Of interest, a report that examined physical outcomes but not cognition before and after PR in COPD patients, found that the small improvement in BBS were not related to improvements of 6MWD.[103] Thus, including balance outcomes, along with usual exercise capacity measures, may be warranted, especially in CI COPD patients.

Aerobic and resistance training

An interesting finding regarding exercise is the enhanced cognitive benefits found in combining aerobic and resistance training versus aerobic training alone in COPD patients.[37] This approach is corroborated by studies of those with stroke[104] and dementia,[105] as well as a meta-analysis of healthy individuals that showed a larger effect size of combined aerobic-resistance training than aerobic training alone.[106]

Working memory training

Cognitive training, specifically WM training, has been recently investigated in COPD patients. While van Beers et al.[72] found an improvement in WM trained task, the improvements did not generalize to overall cognitive improvements as measured by the Cambridge Neuropsychological Test Automated Battery. Additionally, secondary outcomes measuring exercise capacity showed no improvements. A previous study investigating cognitive training in hypoxemic COPD also found no cognitive improvements relative to the control group (no cognitive training).[107] A review investigating cognitive training also affirms that, while cognitive training can improve the specific trained task, there may be a lack of generalizability.[108]

Limitations

There are some limitations in this scoping review. To develop a broader descriptive scope of the differences between CI and CN COPD patients, results from independent t-tests, Mann-Whitney U tests, and correlation coefficients were included. While these results help characterize the relationship between cognition and physical performance, they cannot delineate the underlying mechanisms. Secondly, there was a large degree of heterogeneity in study designs and outcomes that prevented a meta-analysis of the interventions. Moreover, the low statistical power in many of these interventions precludes conclusions of actual treatment effects. Regarding dual task studies, the comparator groups were healthy individuals rather than CN COPD patients, thus the impact CI has on dual tasking cannot be stated. Importantly, most of the data was collected from cross-sectional studies, thus determining the causality between cognition and physical performance is not possible.

Conclusions and future directions

Limited cognitive capacity in COPD was more likely to be associated with impairments in balance, hand function, and dual tasking rather than exercise capacity. Due to the inherent limitations in study design and statistical analysis, causal mechanisms cannot be determined. Pulmonary rehabilitation was the most common treatment, which resulted in variable cognitive improvements. Given the increased incidence of falls in COPD,[109] and the possible relationship between cognitive impairment and balance deficits, future interventions may incorporate balance assessment in COPD patients that present with cognitive decline and impairment.

Authors' contributions

PR, DR and WDR conceived and designed the study. AO-C performed the data base searches. PR, EF, UM, SA, MK, RLFF screened eligibility of titles and abstracts and PR, EF, UM, SA, MK screened for full text exclusion and abstracted data including the quality assessment for the included articles. PR wrote the initial manuscript and WDR contributed to the writing of the manuscript. PR revised the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

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Supplemental Material

Supplemental material for this article is available online.

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