Executive Function, Survival, and Hospitalization in Chronic Obstructive Pulmonary Disease

A Longitudinal Analysis of the National Emphysema Treatment Trial (NETT)

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Abstract

Rationale: Cognitive dysfunction has been demonstrated in chronic obstructive pulmonary disease (COPD), but studies are limited to cross-sectional analyses or incompletely characterized populations.

Objectives: We examined longitudinal changes in sensitive measures of executive function in a well-characterized population of patients with severe COPD.

Methods: This study was performed on patients enrolled in the National Emphysema Treatment Trial. To assess executive function, we analyzed trail making (TM) A and B times at enrollment in the trial (2,128 patients), and at 12 (731 patients) and 24 months (593 patients) after enrollment, adjusted for surgery, marriage status, age, education, income, depression, Pa_{O_2}, Pa_{CO_2}, and smoking. Associations with survival and hospitalizations were examined using Cox regression and linear regression models.

Measurements and Main Results: The average age of the patients was 66.4 years, and the average FEV_1 was 23.9% predicted. At the time of enrolment, 38% had executive dysfunction. Compared with those who did not, these patients were older, less educated, had higher oxygen use, higher Pa_{CO_2}, worse quality of life as measured by the St. George's Respiratory Quotient, reduced well-being, and lower social function. There was no significant change over 2 years in TM A or B times after adjustment for covariables. Changes in TM B times were modestly associated with survival, but changes in TM B − A times were not. Changes in TM scores were not associated with frequency of hospitalization. Lung function, Pa_{O_2}, smoking, survival, and hospitalizations were not significantly different in those with executive dysfunction.

Conclusions: In this large population of patients with severe emphysema and heavy cigarette smoking exposure, there was no significant decline over 2 years in cognitive executive function as measured by TM tests. There was no association between executive function impairment and frequency of hospitalization, and there was a possible modest association with survival. It is plausible that cerebrovascular comorbidities explain previously described cognitive pathology in COPD.

Keywords: chronic obstructive pulmonary disease; cognition; executive function; hospitalization; survival

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*A complete list of members may be found in the Appendix.

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Chronic obstructive pulmonary disease (COPD) is a complex, multisystem disorder. The potential impact of COPD on cognitive ability has an emerging clinical relevance (1–3). Cognitive impairment has been demonstrated in cross-sectional studies of COPD, with moderate to severe impairment in up to 57% of patients hospitalized because of an exacerbation (1). Impairments are often global but most commonly involve executive functions, memory, and attention (4, 5). It has been suggested that impaired cognition may also be a predictor of mortality and disability in certain COPD populations (6, 7). Importantly, cognitive ability is critical for self-management and education, which underpin effective care (8). Understanding of the mechanisms that result in cognitive problems and their clinical impact remain incomplete in COPD.

Mild cognitive impairment has been shown in 36% of patients with moderate to severe COPD (vs. 12% in control subjects) (9). A self-reported diagnosis of COPD in mid-life has been found to be independently associated with subsequent cognitive impairment (hazard ratio, 1.85) (10). In addition, there appears to be a dose–response relationship between COPD duration of more than 5 years at baseline and risk of mild cognitive impairment (11).

Hypoxemia, systemic inflammation, oxidative stress, sympathetic nervous system activation, accelerated aging, and autoimmunity are a selection of plausible pathophysiological mechanisms for brain pathology and cognitive dysfunction in COPD (12). COPD-related cerebrovascular damage has been implicated, with studies showing that impaired lung function is associated with cerebral white matter lesions (13, 14) and the presence of widespread white matter microstructural damage in stable COPD (15). In addition, COPD has been associated with cerebral microbleeds (a marker of cerebral small vessel disease) independent of smoking and cardiovascular risk (16).

In old age, cognitive functioning tends to decline substantially after hospitalization even after controlling for illness severity and prehospital cognitive decline (17). COPD exacerbations have been shown to be associated with myocardial injury and an increased risk of stroke (18, 19). In patients hospitalized with an acute COPD exacerbation, impaired cognitive function is associated with worse health status and longer hospital length of stay (1). We hypothesized that cognitive function would significantly decline over time and that this decline may be associated with disease severity, hospitalizations, and survival. Some of the results of this analysis have been previously reported in the form of an abstract (20).

Methods

The National Institutes of Health–sponsored National Emphysema Treatment Trial (NETT) study protocol is described in detail elsewhere (21). In brief, participants with severe emphysema with no significant comorbid conditions that could interfere with completion of tests, therapy, or follow up were randomized to one of two procedures: lung volume reduction surgery (LVRS) or medical therapy (MT) after completion of a 6- to 10-week pulmonary rehabilitation program.

Trail making (TM) is a sensitive measure of executive function and closely predicts brain damage. Executive function impairment was defined from normative values as time taken to complete TM B of greater than102 seconds (22). Both TM A and B consist of 25 circles that are distributed over a sheet of paper (Figure 1).

In TM A, the circles are numbered from 1 to 25, and the subjects are asked to draw lines that connect the numbers in ascending order. In TM B, circles include both numbers (1–13) and letters (A–L) and are distributed across a sheet of paper. Subjects are asked to draw lines to connect the circles in an ascending sequence alternating between numbers and letters (i.e., 1-A-2-B-3-C). Subjects are instructed to work as quickly as they can, and the number of seconds to complete the task is the final score for each part. The TM B − A score (calculated as the difference between TM-A and TM-B times) is considered a measure of cognitive flexibility relatively independent of manual dexterity (23).

Analysis

Associations between baseline impairment (TM B $>$ 102 s) and other baseline variables were explored using Chi-square tests for categorical variables and Wilcoxon tests for continuous variables. We analyzed TM A and B over time at baseline, 12 months, and 24 months using repeated measures mixed models. Associations of baseline values with survival were explored using Cox proportional hazards models. The relationships between survival and changes in TM scores from baseline to Month 24 were explored using the survival time after Month 24. Survival time was counted from time of the 24-month TM evaluation until the end of the NETT study. The minimum and maximum follow-up time after Month 24 were 1 day and 48 months, respectively, with a median follow up of 18.3 months and a mean (SD) of 19.0 (10.8) months. Associations with hospitalizations and predictors of decline were examined using linear regression models. Relationships between hospitalization and changes in TM scores were modeled using the number of hospitalizations after Month 24. All of the models were adjusted for treatment (surgery vs. others), marital status (married vs. others), education (high school education or less vs. others), income ($<$\$30,000 per year vs. $\geq$\$30,000), age, Beck Depression Inventory, Pa_{O_2}, Pa_{CO_2}, and years smoked.

Results

Baseline Characteristics

Data were available for n = 1,218 subjects at baseline. A total of 731 (60%) subjects had TM data at Month 12, and 593 (49%) had data at Month 24. For the entire cohort of 1,218 subjects, mean age was 66.4 ($\pm$6.1) years, and FEV_1% predicted was 23.9 ($\pm$6.5), consistent with severe airway obstruction. The NETT cohort were heavy smokers with a mean of 64.4 ($\pm$31.2) pack-years. Resting blood oxygen and carbon dioxide levels were in the normal range: Pa_{O_2} 64.4 ($\pm$10.3) mm Hg, Pa_{CO_2} 43.1 ($\pm$5.8) mm Hg, with 51% using supplementary oxygen and reporting a Medical Research Council dyspnea score of 4. Mean 6-minute-walking distance was 368.4 ($\pm$95) meters. A total of 51.9% of the cohort had received a high school education or less.

Average days in hospital after Month 24 was 1.5 ($\pm$4.7), and total number of deaths during follow up was 494 of 1,218 (41%). The 593 patients with TM data at Month 24 had better health at baseline than the patients without TM data. They had significantly lower Beck depression scores,

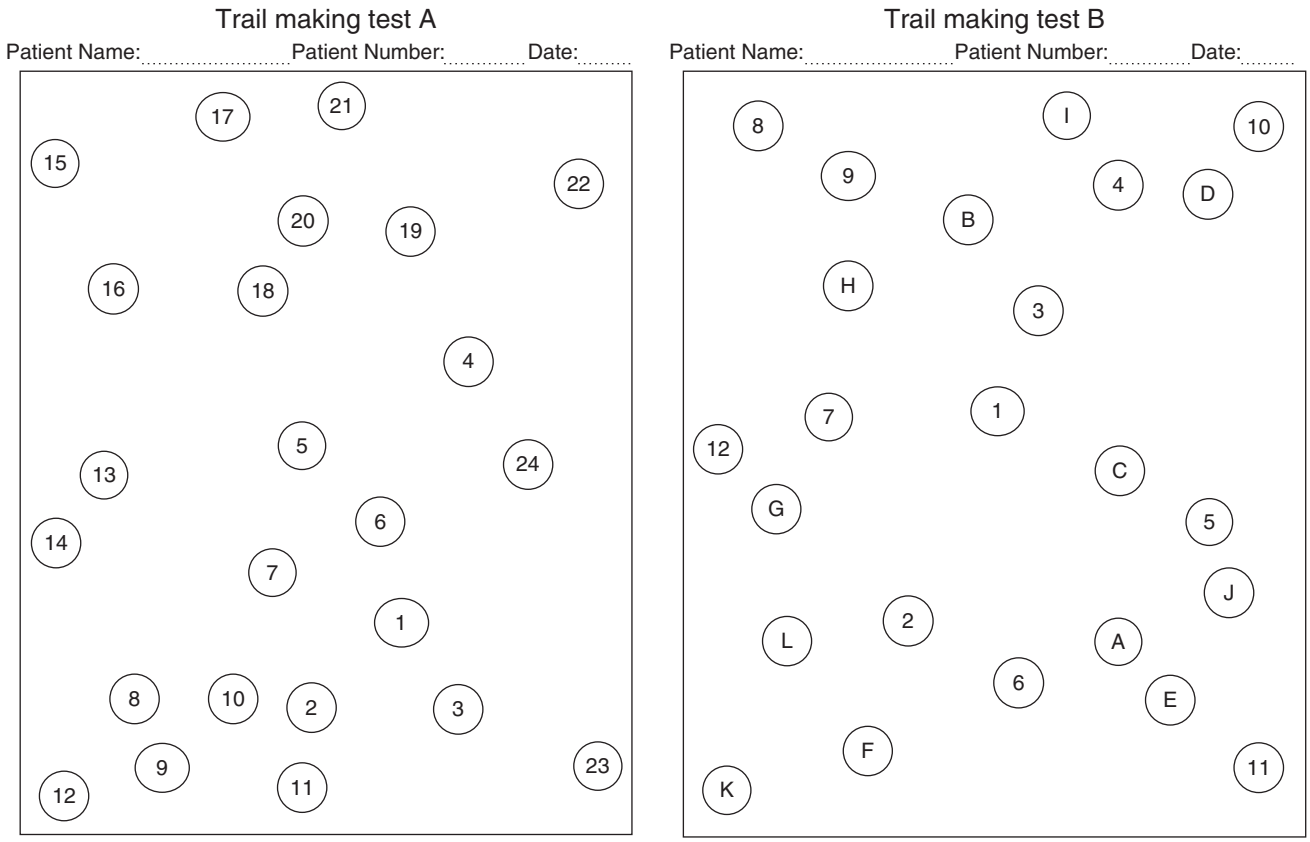

Figure 1. Trail-making tests A and B.

their Pa_{CO_2} scores were about one point lower, and their baseline TM times were significantly lower (Table 1).

Executive Function at Baseline

Thirty-eight percent of patients had impaired executive function at baseline (TM B > 102 s). These individuals were statistically significantly older (67.8 vs. 65.5 yr, $P < 0.001$), had less education, higher Beck depression scores (mean difference of 0.5 points), higher St. George's total scores (54.1 vs. 52.4, $P = 0.016$), were more likely to be using oxygen (56.6 vs. 47.5%, $P = 0.002$), had higher Pa_{CO_2} (43.6 mm Hg vs. 42.9 mm Hg, $P = 0.013$), shorter 6-minute-walking test distance (360 m vs. 373 m, $P = 0.02$), and worse mental well-being, emotional well-being, and social functioning (Table 1).

Longitudinal Change in Executive Function

With 593 patients having longitudinal data, this study had 80% power to detect a 2.1 change in TM A and a 4.3 change in TM B. Plots are shown using all patients (plots using only patients who have data at all three time points gave similar results; *see* online supplement).

TM A showed a reduction in time taken of about 4 seconds (improvement) over 2 years. TM B and TM B − A show an increase in time taken to complete after the first year (decline in function) but a reduction in time taken (improvement in function) in the second year (Figure 2).

Repeated measures models for change in cognition over time is a sensitive model for looking at scores over time. It takes into account the correlation between measures on the same person. In these models, scores for TM A and TM B were significantly lower than baseline at 2 years (Table 2), indicating at least no worsening or decline in executive function over time. A multiple linear regression model was also used to assess change in executive function using change in TM as dependent variables; this also showed no significant change in TM after adjusting for other variables (*see* online supplement).

Executive Function and Survival

There was no significant difference in survival between patients with executive dysfunction (TM B > 102 s) and other patients (Table 3). We also looked at associations between survival and changes in TM scores after adjusting for other variables. Changes in TM B and TM A from baseline to 2 years were related to survival after Year 2 (an increase in TM B by 1 s was associated with a 1% increased hazard of death). However, changes TM B − A were not related to survival (*see* the online supplement).

Executive Function and Hospitalization

There was no significant difference in hospitalizations between patients with executive dysfunction (TM B > 102 s) and other patients (Table 3). We used models to look at whether changes in TM can predict the number of hospitalizations after the change (e.g., changes in TM B from baseline to 2 years was used to predict the number of hospitalizations after 2 years).

Table 1. Baseline characteristics

	Baseline Trail, B > 102 (*N = 463*)	Baseline Trail, B ⩽ 102 (*N = 755*)	Total (*N = 1,218*)	*P* Value
Medical, yes	230 (49.7%)	380 (50.3%)	610 (50.1%)	0.8243
Married, yes	306 (66.1%)	483 (64.0%)	789 (64.8%)	0.4527
Age, mean (SD), yr	67.8 (5.6)	65.5 (6.3)	66.4 (6.1)	**<0.0001**
High school education or less	279 (60.3%)	353 (46.8%)	632 (51.9%)	**<0.0001**
Income < $30, 000				
Missing	3	9	12	0.0798
N (%)	260 (56.5%)	383 (51.3%)	643 (53.3%)	
MRC Scale: missing	1	1	2	0.3542
0	6 (1.3%)	12 (1.6%)	18 (1.5%)	
1	3 (0.6%)	1 (0.1%)	4 (0.3%)	
2	127 (27.5%)	185 (24.5%)	312 (25.7%)	
3	92 (19.9%)	170 (22.5%)	262 (21.5%)	
4	234 (50.6%)	386 (51.2%)	620 (51.0%)	
Oxygen used at rest	262 (56.6%)	359 (47.5%)	621 (51.0%)	**0.0022**
Disability	0.1 (0.2)	0.0 (0.2)	0.0 (0.2)	0.6657
BDI				
Mean (SD)	3.9 (3.8)	3.4 (3.5)	3.6 (3.6)	**0.0138**
Median	3.0	3.0	3.0	
Pa_{O_2}, mm Hg				
N	462	755	1217	0.2776
Mean (SD)	64.0 (10.2)	64.6 (10.3)	64.4 (10.3)	
Pa_{CO_2}, mm Hg				
N	462	755	1217	**0.0126**
Mean (SD)	43.6 (5.7)	42.9 (5.9)	43.1 (5.8)	
Pre FEV_1% predicted				
N	463	753	1216	0.6420
Mean (SD)	23.8 (6.6)	24.0 (6.5)	23.9 (6.5)	
Years smoked times cigarettes smoked per day	1,300.0 (642.4)	1,279.7 (612.2)	1,287.4 (623.6)	0.7900
6-min-walk distance, ft	1,184.2 (319.8)	1,223.6 (308.3)	1,208.6 (313.2)	**0.0244**
SGRQ total				**0.0156**
N	463	754	1217	
Mean (SD)	54.1 (13.2)	52.4 (12.3)	53.1 (12.7)	

Definition of abbreviations: BDI = Beck Depression Inventory; MRC = Medical Research Council; SGRQ = St. George's Respiratory Questionnaire. Bold text indicates $P < 0.02$.

None of the change variables were related to number of hospitalizations after adjusting for baseline TM score, surgery, marital status, age, education, income, depression, Pa_{O_2}, Pa_{CO_2}, and years smoked (*see* online supplement).

Discussion

This analysis represents the first longitudinal study of executive function and clinical outcomes in a large and well-characterized COPD cohort. It suggests that in patients with severe emphysema and heavy smoking exposure, executive dysfunction is present, but there is no significant decline in executive ability over 2 years after adjusting for other variables. Although change in executive function over 2 years was modestly associated with survival (increased TM B by 1 s associated with 1% increased hazard of death), changes in TM B − A suggested that the association is not specifically related to cognitive function but rather to the lack of manual dexterity required to complete the assessment. No association was found between executive function and hospitalization.

Our finding that 38% of the patients in the NETT cohort had executive dysfunction at baseline is similar to the prevalence of mild cognitive impairment in a previous, small cross-sectional study of individuals with moderate to severe COPD (36%). Fewer NETT patients had executive dysfunction than has been reported for patients with COPD with more severe hypoxemia or during hospitalization for an exacerbation of COPD (57–61%) (1, 24).

Patients in our study with executive dysfunction tended to be older and less educated than those without; however, many of the differences were not clinically significant, with the exception of health status. Notably, lung function, Pa_{O_2}, smoking exposure, survival, and hospitalizations were not significantly different in those with executive dysfunction. There are mixed results from other studies that have examined correlations between cognitive performance and disease severity measures in COPD, such as lung function and hypoxemia. Some suggest associations are weak (4, 24); others have demonstrated significant correlations and a more rapid cognitive decline in the presence of hypoxemia (25, 26). We found no association between executive function with either hypoxemia or hypercapnia.

The relationship between cognitive function and health status has been studied (24, 27). The Sickness Impact Profile (SIP) correlates moderately with cognitive function ($r = 0.37$–0.45, $P < 0.01$) in both hypoxemic (28) and nonhypoxemic patients ($r = -0.62$, $P = 0.005$) (27). The relationship between severity of depression and cognitive dysfunction has also been examined in a metaanalysis, which found

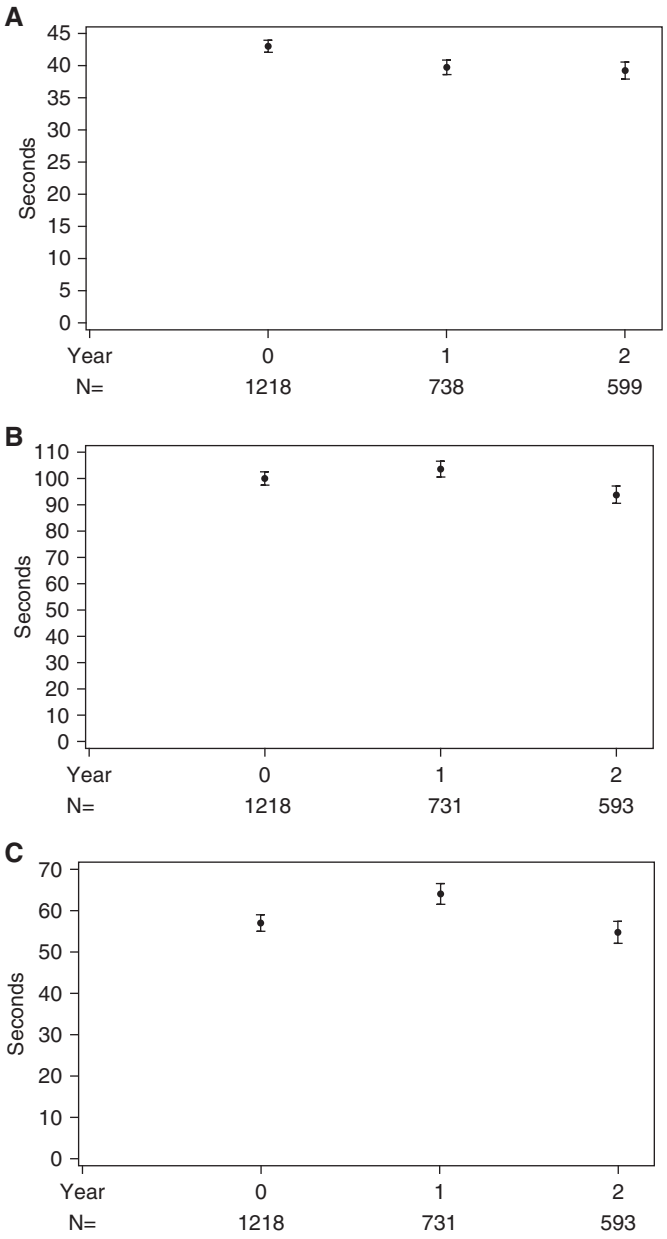

Figure 2. Changes in trail making (TM) over 2 years. (*A*) TM A time; (*B*) TM B time; (*C*) TM B − A time.

that episodic memory, executive function, and processing speed all correlated with severity of depression, but the correlations were relatively small (<10% shared variance) (29). In this study we found differences in depression scores and quality-of-life scores between individuals with and without abnormal TM tests were not clinically significant.

Mechanisms

The NETT cohort provides a unique experimental opportunity to advance our understanding of the mechanisms that underlie cognitive problems and their clinical impact in COPD. We have been able to examine the contribution of impaired lung function, smoking, and hypoxemia in the absence of significant comorbidities over a prolonged follow up. Our results indicate that COPD disease severity by itself is not independently associated with the development of executive dysfunction. Importantly also, this study demonstrates that in patients with COPD there is no significant association between executive function and hospitalization and no meaningful association with survival.It is possible that the observed cognitive impairment present in the absence of a significant decline in cognition during the study period may result from preexisting cognitive impairment or a decline process occurring earlier in the disease. There are some data to support this with mid-life impaired lung function associated with subsequent risk of cognitive impairment (10), but we would still expect to see some signal to indicate ongoing cognitive decline over a 2-year period in such a large sample if this were the case. Data from the Health and Retirement Study showed a greater decline in cognitive function in people with self-reported severe COPD (25), but this group had a greater chronic disease burden, with significantly higher rates of comorbid hypertension and stroke. Also, considering recent neuroimaging studies that point to cerebrovascular damage (15, 16), it is plausible that cerebrovascular comorbidities (significantly absent from this highly selected cohort) explain much of the cognitive pathology observed in patients with COPD.

Hospitalizations

Neither executive dysfunction at baseline nor changes in executive function over time were associated with hospitalization rates. This suggests that cognitive dysfunction is not a significant risk factor for hospitalization in this population and does not lend support to the hypothesis that exacerbations result in cognitive impairment. It is possible that either hospitalizations are truly not associated with cognitive decline or that there were insufficient events to demonstrate a relationship, given that the average number of days hospitalized during 2 years was low (mean, 1.5 d; median, 0 d).

Survival

Our findings on survival are novel, as no other study to date has the degree of characterization of enrolled patients with COPD and the 2-year follow-up data that we present in this study. TM B (letters and numbers) had equivocal results, as it was not significantly associated with survival in the first year but was modestly (at best) associated with survival in the second year. Although there was an increase in the TM B scores (overall decline in function) at year 1, the scores decrease (overall improve in

Table 2. Repeated measures models for trail making over time

Endpoint	Variable	Estimate	*P* Value
Trail making A	Intercept	−1.0	0.8949
	Year 0	—	—
	Year 1 (vs. Year 0)	−2.2	<0.0001
	Year 2 (vs. Year 0)	−3.0	<0.0001
	Medical treatment	0.3	0.7530
	Married	1.0	0.2616
	Age	0.6	<0.0001
	High school education or less	3.7	<0.0001
	Income < $30,000	0.5	0.6094
	Beck Depression Inventory	0.3	0.0059
	Pa_{O_2}	−0.019	0.6681
	Pa_{CO_2}	0.103	0.1902
	Years smoked times cigarettes per day	0.00002	0.9824
Trail making B	Intercept	−56.7	0.0031
	Year 0	—	—
	Year 1 (vs. Year 0)	5.8	<0.0001
	Year 2 (vs. Year 0)	−3.3	0.0237
	Medical treatment	0.4	0.8344
	Married	1.8	0.4619
	Age	1.8	<0.0001
	High school education or less	15.6	<0.0001
	Income <$30,000	3.0	0.1989
	Beck Depression Inventory	1.0	0.0004
	Pa_{O_2}	0.056	0.6222
	Pa_{CO_2}	0.503	0.0134
	Years smoked times cigarettes per day	−0.001	0.4308

function) at year 2 below the baseline levels. TM B − A was not associated with survival. Based on our results, executive function is not meaningfully associated with survival in patients with COPD.

Strengths and Limitations of This Work

This study represents the strongest of its kind to shed light into the association of cognitive impairment and meaningful outcomes in COPD, such as hospitalizations and survival. The latter is based on several aspects that make this study unique: first, detailed characterization of the individuals based on physiological tests versus self-report of COPD status (11, 25), and second, the follow-up time of 2 years in a large cohort that we consider sufficient to formulate our conclusions.

Although the TM tests may not provide the most comprehensive assessment of cognitive function, collectively they do provide a most sensitive and accurate measure of executive function (the cognitive domain most frequently and severely affected in COPD). The lack of a control group is a weakness of this study, which is partly counterbalanced by our large number, comprehensively characterized, longitudinal data and in-depth analysis.

Another important limitation of this study is that changes in TM scores were not available for all subjects. Subjects with TM scores at Month 24 had less severe disease than all 1,218 subjects who started the study, although analysis was performed on all patients and those with data at 24 months with no significant difference (*see* online supplement).

Conclusions

In this large population of patients with severe emphysema and heavy smoking

Table 3. Survival by baseline executive dysfunction

Variable	N	Events, n (%)	Median Days	Cox Multivariate Hazard Ratio (95% CI)	Cox Multivariate Likelihood Ratio *P* Value (*n = 1,205*)
Trail making B time, s					0.7235
Baseline trail B > 102	463	199 (43)	1,549	1.03 (0.86–1.25)	
Baseline trail B ⩽ 102	755	295 (39)	1,562	—	
Medical					0.1987
No	608	233 (38)	1,640	—	
Yes	610	261 (43)	1,482	1.13 (0.94–1.35)	
Married					0.5320
No	429	173 (40)	1,448	—	
Yes	789	321 (41)	1,600	0.94 (0.77–1.15)	
High school education or less					0.9704
No	586	239 (41)	1,538	—	
Yes	632	255 (40)	1,594	1.00 (0.82–1.21)	
Income < $30,000					0.5314
No	563	222 (39)	1,643	—	
Yes	643	268 (42)	1,489	1.07 (0.87–1.30)	
Age	1,218	494 (41)	1,562	1.015 (0.998–1.031)	0.0797
Beck Depression Inventory: baseline	1,218	494 (41)	1,562	1.019 (0.994–1.044)	0.1405
Pa_{O_2}: baseline	1,217	494 (41)	1,562	0.993 (0.983–1.002)	0.1402
Pa_{CO_2}: baseline	1,217	494 (41)	1,562	1.029 (1.012–1.046)	0.0006
Years smoked times cigarettes smoked per day: baseline	1,218	494 (41)	1,562	1.0000 (0.9999–1.0002)	0.6707

Definition of abbreviation: CI = confidence interval

exposure, there was no significant impairment or decline over 2 years in executive function after comprehensive adjustment for confounders. There was no association between executive function and hospitalizations and a possible modest (at best) association with survival.

Smoking and disease severity measures alone did not appear to explain executive function impairment. It is plausible that cerebrovascular comorbidities rather than lung function, smoking, and hypoxemia explain previously described cognitive pathology in COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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