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Airway wall thickness and PRISm are associated with cognitive impairment in individuals with cigarette smoking exposure

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Abstract

Background Individuals with chronic obstructive pulmonary disease (COPD) and cigarette smoking exposure are at increased risk of cognitive impairment; however, the clinical characteristics of those at risk are incompletely understood.

Methods We conducted a secondary analysis of COPDGene cohort data to identify clinical characteristics, particularly pulmonary function and lung CT metrics, associated with cognitive impairment. Cognitive items available from Phase 3 included: self-report of a cognitive disorder diagnosis and cognitive difficulties, and probable cognitive impairment (pCI) defined by Mini-Cog ≤ 3. Thirty-seven variables were considered for inclusion in a mixed effects logistic regression with pCI as the dependent variable including demographics, smoking history, medical history, symptom severity, pulmonary function testing, and COPD-related lung CT variables.

Results Among 2,079 participants (mean age = 68.7[SD ± 8.6] years, 51.2% female, 28.7% African American), the frequency of pCI differed by smoking/COPD severity group (9.4% never smokers, 18.7% smoking history-normal spirometry, 30.0% preserved ratio impaired spirometry [PRISm], 26.3% GOLD 1–4; $p < 0.001$). Older age, male sex, lower education, African American race, lower body mass index, higher anxiety symptoms, and CT metrics (higher Perc15 and Pi10) were associated with pCI in the final model.

Conclusions Just under thirty percent of participants with smoking exposure and evidence of lung disease on spirometry (PRISm or GOLD 1–4) had pCI, with the highest frequency in PRISm and advanced COPD. Several demographic and clinical characteristics were associated with pCI including airway disease measured via Pi10 on lung CT pointing to a potential link between specific COPD-related physiology and cognitive impairment.

Keywords Mini-Cog, Cognition, Airway wall thickness, Cigarette smoking

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Background

Individuals with chronic obstructive pulmonary disease (COPD) are at increased risk for cognitive impairment [1] with meta-analysis finding that approximately 30% of patients have evidence of cognitive impairment [2]. Prevalence is higher when using more sensitive domain specific neuropsychological tests or when targeting patients during or soon after hospitalization for an exacerbation [3]. The presence of COPD has been prospectively associated with new onset mild cognitive impairment (MCI) during the subsequent 5 years, with a dose-response relationship between COPD duration and risk [4]. Cognitive impairment is impactful as it has been associated with reduced quality of life [5], limited independence in daily functioning [6, 7], difficulty with medication adherence [8], errors with respiratory inhaler medication technique [9, 10], risk for exacerbations [11], and mortality during hospitalization in COPD [12].

Identifying which individuals are at risk for COPD-related cognitive impairment is important to guide clinical monitoring and inform future mechanistic studies. The presence of advanced COPD (classified using traditional GOLD spirometric criteria) and hypoxemia are well known risk factors for cognitive impairment [3, 13–16]; however, some patients experience cognitive impairment in the absence of hypoxemia earlier in disease progression [17, 18]. In response to calls to examine a wider range of clinical measures [19, 20], studies over the past decade have examined comorbidities including cardiovascular disease [21] and COPD/sleep apnea overlap syndrome [22–24] and their association with cognition. There is also increasing evidence that many people with smoking exposure show lung changes and experience clinical symptoms before they meet criteria for COPD diagnosis based on spirometry [25–27]. Preserved ratio impaired spirometry (PRISm; defined as reduced forced expiratory volume in 1 s (FEV1) in the context of preserved FEV1/forced vital capacity (FVC)) has been associated with adverse clinical outcomes including mortality and hospitalizations [28–30]. PRISm has also been associated with systemic inflammation and increased prevalence of metabolic disease including diabetes and cardiovascular comorbidities [31–34]. Collectively, these findings suggest that it is important to include a range of individuals, including those at risk for COPD due to prior smoking exposure and those with advanced COPD, in research focused on cognition in order to capture the full spectrum of disease.

The goals of the current analysis were two-fold. First, we described the prevalence of self-reported cognitive difficulties and objectively assessed probable cognitive impairment (pCI) in a cohort of older adults enriched for a history of smoking exposure and spanning the spectrum of COPD severity (defined by Global Initiative for Chronic Obstructive Lung Disease [GOLD] [1] and Preserved Ratio Impaired Spirometry [PRISm] [35]). Second, we identified demographic and clinical characteristics associated with pCI. We hypothesized that participants with PRISm and GOLD 1–4 COPD would have higher rates of pCI than participants without spirometric evidence of lung disease. In addition to demographics (e.g., older age, lower education) and medical comorbidities (e.g., cardiovascular disease and sleep apnea), we hypothesized that structural abnormalities in the lung assessed using CT would be associated with pCI. We reasoned that since structural abnormalities on CT have been associated with inflammation and other mechanisms [36] likely to have systemic effects, lung CT measures may be more strongly associated with pCI than spirometric impairment.

Methods

Cohort

COPDGene is a longitudinal, observational cohort study that enrolled Non-Hispanic white and African American individuals with ≥ 10 pack-years of cigarette smoking exposure across 21 US centers [37]. A smaller group of never smoking controls were also enrolled. Data collection has occurred across three phases with visits approximately every five years. Data reported here were collected at in person Phase 3 (10-year follow-up) visits from 2018-2020, prior to the COVID-19 pandemic.

Measures

Cognition

COPDGene Phase 3 included two self-report questions about cognition and the Mini-Cog. Self-report included: (1) prior diagnosis by a physician with a cognitive disorder, and (2) perceived confusion or memory loss "that is happening more often or is getting worse" over the previous 12 months [38, 39].

The Mini-Cog [40, 41] is a standardized, validated screening tool that takes 3–5-minutes to administer and involves two tasks: 3-word recall and clock drawing. Prior to Phase 3, research coordinators were provided training on administration and scoring of the Mini-Cog via webinar, with a recording of the training available throughout the study. Word list 1 (banana, sunrise, and chair) was employed [42]. Total Mini-Cog scores range from 0 to 5, with one point for each of the 3 words immediately correctly recalled and a score of either 0 or 2 for Clock Drawing based on standardized criteria [43]. Scores were entered by site coordinators into a REDCap database [44, 45] with an upload of Clock Drawing, which was re-scored by an adjudication team who coded Clock Drawing error types (Appendix B). The cohort was categorized into two groups using a cut point to maximize sensitivity based on prior research [38]:

Table 1 Demographic and clinical characteristics for all participants and the two Mini-Cog defined groups: Low cognitive risk and Probable Cognitive Impairment (pCI) (*N* = 2079)

Variable [*n*][1]		Characteristics for All Participants[2]	Low Cognitive Risk (Mini-Cog 4–5)	Probable Cognitive Impairment (Mini-Cog ≤ 3)
Age [*n = 2079*]		68.7 (8.6)	68.5 (8.4)	69.4 (9.2)
Sex [*n = 2079*]	Female	1065 (51.2%)	849 (79.7%)	216 (20.3%)
	Male	1014 (48.8%)	754 (74.4%)	260 (25.6%)
Race [*n = 2079*]	Non-Hispanic White (NHW)	1483 (71.3%)	1208 (81.5%)	275 (18.5%)
	African American (AA)	596 (28.7%)	395 (66.3%)	201 (33.7%)
Education [*n = 2001*]	< High School (HS)	205 (10.2%)	122 (59.5%)	83 (40.5%)
	HS Graduate or GED	434 (21.7%)	314 (72.4%)	120 (27.6%)
	Some College and Above	1362 (68.1%)	1096 (80.5%)	266 (19.5%)
Income [*n = 2077*]	< $15,000	411 (19.8%)	287 (69.8%)	124 (30.2%)
	$15,000-$35,000	432 (20.8%)	330 (76.4%)	102 (23.6%)
	$35,000-$50,000	284 (13.7%)	230 (81.0%)	54 (19.0%)
	$50,000-$75,000	276 (13.3%)	234 (84.8%)	42 (15.2%)
	> $75,000	295 (14.2%)	256 (86.8%)	39 (13.2%)
	Decline to answer	379 (18.2%)	265 (69.9%)	114 (30.1%)
Coupled [*n = 2077*]	Yes	903 (43.5%)	731 (81.0%)	172 (19.0%)
	No	1174 (56.5%)	871 (74.2%)	303 (25.8%)
ATS Packyears [*n = 2077*]		41.9 (24.7)	41.0 (24.4)	44.7 (25.4)
Smoking Status [*n = 2079*]	Never	153 (7.4%)	129 (84.3%)	24 (15.7%)
	Former	1273 (61.2%)	1001 (78.6%)	272 (21.4%)
	Current	653 (31.4%)	473 (72.4%)	180 (27.6%)
Airflow Limitation/COPD GOLD Group [*n = 2079*]	Never Smokers	106 (5.1%)	96 (90.6%)	10 (9.4%)
	Smoking History-Normal Spirometry	812 (39.1%)	660 (81.3%)	152 (18.7%)
	PRISm	237 (11.4%)	166 (70.0%)	71 (30.0%)
	GOLD 1	240 (11.5%)	175 (72.9%)	65 (27.1%)
	GOLD 2	385 (18.5%)	286 (74.3%)	99 (25.7%)
	GOLD 3	193 (9.3%)	146 (75.6%)	47 (24.4%)
	GOLD 4	106 (5.1%)	74 (69.8%)	32 (30.2%)
Spirometry: FEV_1% predicted [*n = 2079*]		79.8 (26.1)	80.9 (25.8)	75.9 (26.7)
Diffusion Capacity for Carbon Monoxide (DLCO) [*n = 1700*]		22.4 (4.0)	22.3 (4.0)	22.4 (4.0)
Resting SaO2 [*n = 2068*]		96.1 (2.7)	96.1 (2.7)	96.0 (2.8)
COPD Assessment Test (CAT) Total Score [*n = 2079*]		11.0 (8.3)	10.6 (8.1)	12.4 (8.7)
Severe exacerbation in last year [*n = 2079*]	Yes	173 (8.3%)	115 (66.5%)	58 (33.5%)
	No	1906 (91.7%)	1488 (78.1%)	418 (21.9%)
Dyspnea (mMRC ≥ 2) [*n = 2079*]	Yes	759 (36.5%)	561 (73.9%)	198 (26.1%)
	No	1320 (63.5%)	1042 (78.9%)	278 (21.1%)
6 min Walk Test (distance in meters) [*n = 1954*]		1310.9 (413.2)	1340.9 (411.6)	1206.1 (402.1)
Total Lung Capacity: [*n = 1961*]		5.3 (1.4)	5.4 (1.4)	5.2 (1.4)

Table 1 (continued)

Variable [*n*][1]		Characteristics for All Participants[2]	Low Cognitive Risk (Mini-Cog 4–5)	Probable Cognitive Impairment (Mini-Cog ≤ 3)
$LAA\text{-}856_E$ [*n = 1604*]		22.7 (19.2)	22.3 (19.0)	23.9 (20.0)
Perc15 [*n = 1961*]		-927.7 (30.0)	-928.7 (28.9)	-924.6 (33.1)
Pi10 [*n = 1928*]		2.3 (0.6)	2.3 (0.6)	2.4 (0.6)
Systolic Blood Pressure (in mmHg) [*n = 2078*]		130.2 (17.3)	130.0 (17.3)	130.8 (17.3)
Body Mass Index (BMI; kg/m^2) [*n = 2079*]		28.6 (6.2)	28.7 (6.2)	28.2 (6.5)
Hospital Anxiety and Depression Scale-Anxiety Symptoms (HADS-A) [*n = 2078*]		3.8 (3.5)	3.6 (3.4)	4.4 (3.9)
Hospital Anxiety and Depression Scale- Depressive Symptoms (HADS-D) [*n = 2078*]		3.2 (3.1)	3.0 (3.0)	3.7 (3.4)
Duke Activity Status Index (DASI) [*n = 2079*]		40.6 (16.1)	41.5 (15.9)	37.7 (16.6)
Depressive Disorder [*n = 2079*]	Yes	535 (25.7%)	410 (76.6%)	125 (23.4%)
	No	1544 (74.3%)	1193 (77.3%)	351 (22.7%)
Anxiety Disorder [*n = 2079*]	Yes	414 (19.9%)	312 (75.4%)	102 (24.6%)
	No	1665 (80.1%)	1291 (77.5%)	374 (22.5%)
Stroke [*n = 2079*]	Yes	100 (4.8%)	74 (74.0%)	26 (26.0%)
	No	1979 (95.2%)	1529 (77.3%)	450 (22.7%)
Diabetes [*n = 2079*]	Yes	427 (20.5%)	311 (72.8%)	116 (27.2%)
	No	1652 (79.5%)	1292 (78.2%)	360 (21.8%)
Kidney Disease [*n = 2079*]	Yes	94 (4.5%)	65 (69.1%)	29 (30.9%)
	No	1985 (95.5%)	1538 (77.5%)	447 (22.5%)
Liver Disease [*n = 2079*]	Yes	98 (4.7%)	72 (73.5%)	26 (26.5%)
	No	1981 (95.3%)	1531 (77.3%)	450 (22.7%)
Obstructive Sleep Apnea [*n = 2079*]	Yes	560 (26.9%)	433 (77.3%)	127 (22.7%)
	No	1519 (73.1%)	1170 (77.0%)	349 (23.0%)
Hypertension [*n = 2079*]	Yes	1183 (56.9%)	885 (74.8%)	298 (25.2%)
	No	896 (43.1%)	718 (80.1%)	178 (19.9%)
Congestive Heart Failure (CHF) [*n = 2079*]	Yes	93 (4.5%)	71 (76.3%)	22 (23.7%)
	No	1986 (95.5%)	1532 (77.1%)	454 (22.9%)
Atrial Fibrillation (Afib) [*n = 2079*]	Yes	153 (7.4%)	109 (71.2%)	44 (28.8%)
	No	1926 (92.6%)	1494 (77.6%)	432 (22.4%)
Coronary Artery Disease (CAD) [*n = 2079*]	Yes	332 (16.0%)	254 (76.5%)	78 (23.5%)
	No	1747 (84.0%)	1349 (77.2%)	398 (22.8%)
Peripheral Vascular Disease (PVD) [*n = 2079*]	Yes	84 (4.0%)	56 (66.7%)	28 (33.3%)
	No	1995 (96.0%)	1547 (77.5%)	448 (22.5%)

[1]: [*n*] was total non-missing values for the variables. Most variables had no missing values with only DLCO and $LAA\text{-}856_E$ on lung CT missing > 10%

[2]: mean (standard deviation) listed for continuous variables and total non-missing values (%) by level of categorical variables

- *"Probable cognitive impairment"(pCI)* = Mini-Cog total ≤ 3; and
- *"Low cognitive impairment risk"* = Mini-Cog total of 4–5

This cut point has been used in several large descriptive studies with evidence to support that it identifies individuals with milder cognitive impairment at earlier stages, as compared to the originally validated dementia cut point of ≤ 2 [42, 46].

Demographic and clinical characteristics

Demographics and smoking history were obtained via self-report. Clinical measures included post-bronchodilator spirometry, systolic blood pressure, blood oxygen saturation (SpO_2), diffusion capacity for carbon monoxide (DLCO), body mass index (BMI; weight [kg]/height^2[m]),

and 6-minute walk test. Questionnaires assessed functional capacity (Duke Activity Status Index[DASI] [47]), anxiety and depression (Hospital Anxiety and Depression Scale[HADS-A and HADS-D] [48]), lifetime problematic alcohol use (CAGE Substance Abuse Screening Tool ≥ 2) [49], dyspnea (modified Medical Research Council[mMRC] Dyspnea Scale ≥ 2) and impact of COPD (COPD Assessment Test[CAT]). Severe COPD exacerbations in the prior year were defined via self-report of an emergency room visit or hospitalization due to flare-up of COPD. Medical history was self-reported at Phases 1–3 and items in the analysis reflect report at any Phase.

Participants were grouped into smoking status/COPD groups (at Phase 3) including: Never Smokers, Normal Spirometry (smoking history with FEV1/FVC≥0.70 and FEV1%predicted ≥ 80), preserved ratio impaired spirometry (PRISm; smoking history with FEV1/FVC≥0.70 and FEV1%predicted < 80) and GOLD spirometry stage (GOLD 1-4 [50]).

Lung CT measures

COPDGene CT acquisition and quantification methods have been previously published [37]. Coached, full inspiratory and expiratory lung CT data were collected at Phase 3 with a low dose protocol (mean effective radiation of 1.5 mSv ± 0.7) [51]. We included three CT measures processed using Thirona software to reflect key components of COPD. First, we included % voxels≤-856 Hounsfield units (HU) on the expiratory scan referred to as low attenuation area ($LAA\text{-}856_E$) to capture gas trapping, thought to reflect small airway dysfunction. Second, lung density was assessed on inspiratory CT using Perc15, the HU value at the 15th percentile of the lung CT histogram, often used as a marker of emphysema [52]. Finally, Pi10 was included as a measure of airway wall thickness relative to luminal area based on all segmented airways and defined as the square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm [53]. Strong repeatability of these measures has been demonstrated [54].

Statistical analysis

Participant characteristics and probable cognitive impairment (pCI)

Candidate variable selection and pruning

Prior to analysis we identified 37 variables with potentially meaningful relationships with cognitive impairment selected via literature review and investigator expertise. The variables, presented in Table 1, fell into eight general domains: demographics, smoking history, COPD status and symptom severity, lung CT measures, physical measures (e.g., blood pressure), symptoms of depression and anxiety, functional capacity, and medical history. We used forward stepwise logistic regression and an alpha of 0.20 to prune from the list of 37 candidate variables those that had minimal evidence of an association with pCI. This approach prevented removing participants due to missing measurements on variables that were unlikely to meet the inclusion criteria in our final regression model, while maintaining a broader set of variables for exploratory network analysis.

Exploratory network analysis using a mixed graphical model

A mixed graphical model (MGM) was fit for the variables that survived pruning and pCI. Using participants with complete data for these variables, the MGM estimated the complete network of dependencies (strength of associations) between each variable pair after accounting for the other variables and their pairwise interactions. Ranking the dependencies provides network level insight into the strongest pairs and clusters of related variables. MGMs do not estimate variables' effect on one outcome; therefore, the most accurate identification of candidates associated with pCI was through logistic regression.

Mixed effects logistic regression model

After we estimated the final logistic model as described above, we fit a mixed effects logistic model with pCI as the outcome via backwards selection applied to the pruned list of candidate variables with a 0.05 p-value threshold. Study site was included as a random effect and continuous variables were standardized to improve model convergence. All two-way interactions were evaluated for inclusion using forward selection.

R version 4.4.1 was used for all analyses. The MGM was generated with the mgm package [55], with results visualized using the ggplot2, qgraph, and wesanderson packages [56–58]. Mixed effect logistic model estimation and evaluation used the lmer and influence.ME packages [57]. A 5% significance threshold was used in hypothesis testing, and 95% confidence intervals are two-sided.

Prevalence of self-reported cognitive difficulties and probable cognitive impairment (pCI)

Frequencies of the two self-reported measures of cognitive difficulties (prior diagnosis and worsening confusion/memory loss) were calculated and compared to pCI via Mini-Cog using McNemar's Chi-squared test. Prevalences of pCI via Mini-Cog were compared across smoking/COPD groups using Chi-squared tests. Frequencies of Clock Drawing error types were calculated to identify common errors and quantify differences in error type between smoking/COPD groups using Chi-squared tests.

Results

Participants

The sample included COPDGene participants who completed in-person Phase 3 study visits from 2018-2020 prior to the COVID-19 pandemic with complete Mini-Cog data. Of the 2,079 in the study sample, 1,991 has a history of cigarette smoking (i.e., were current or former smokers with at least a 10 pack-year history) and 106 were never smokers who did not meet spirometric criteria for COPD. More specifically, there were 924 individuals with a history of smoking who had GOLD 1–4 COPD, 237 individuals with a history of smoking who had a PRISm pattern on spirometry, 812 individuals with a history of smoking who had normal spirometry, and 106 never smokers who did not meet spirometric criteria for COPD. The sample was approximately 69 years old and approximately half were female. Just under one third of the sample were African American, with two thirds non-Hispanic Whites. Table 1 summarizes the demographic and clinical characteristics of the sample.

Frequencies of probable cognitive impairment and self-reported cognitive difficulties

Frequencies of pCI and self-reported cognitive items are shown in Table 1. 27.0% (314/1,161) of participants with a history of smoking exposure and evidence of lung disease on spirometry (PRISm or GOLD 1–4) had pCI, as compared to 17.6% (162/918) for Smoking Exposure-Normal Spirometry ($p < 0.001$). The highest frequencies of pCI were in PRISm (30.0%) and GOLD 4 (30.2%). Both Word Recall and Clock Drawing scores differed across smoking/COPD groups (Supplementary Table 1). The most common Clock Drawing error was time set incorrectly (at 9%), which was statistically significantly different across smoking/COPD groups ($p = 0.02$; Supplemental Table 2).

Only 3.8% (79/2,060) of the sample reported a previous clinical diagnosis of a cognitive disorder (Table 2). 44% of those individuals were classified as having pCI (35/79 44.3%) via Mini-Cog, indicating inconsistency between prior diagnosis and current objective assessment ($p < 0.001$).

Mixed graphical modeling links to probable cognitive impairment

The application of forward stepwise logistic regression pruned the original 37 candidate demographic and clinical variables to 14 (see Supplemental Fig. 1's legend). A mixed graphical model (MGM) was fit for the 14 variables and pCI, which were in mixed formats (categorical [binary, multilevel] and continuous). In Supplemental Fig. 1 variables are depicted as nodes and colored by domain. pCI is featured with a diamond and the top 50% of dependencies are shown.

The MGM depicts the strongest candidates associated with pCI and their inter-connectedness in a network structure. The variables with strong dependencies included demographics (age, gender, race, education, and income), clinical variables (Pi10, severe exacerbations, and a subset of medical history variables (peripheral vascular disease[PVD], coronary artery disease [CAD], and kidney disease). The MGM suggests that some candidate variables may impact PCI in a complicated way; for example, Perc15 (node #8) had a strong association with some demographic variables that were linked to pCI.

Logistic regression modeling probable cognitive impairment

The final mixed effects logistic regression model (Table 3) included 8 variables and one interaction term with area under the curve of 0.69 (95% bootstrap confidence interval [0.66,0.72]). The model had no collinearity, influential observation, or logit assumption issues. Race was the strongest predictor with African American participants having 2.36 times the odds of pCI than Non-Hispanic Whites (95% CI: [1.74,3.21]). Older age, higher Perc15, higher Pi10, and higher HADS-A score were associated with *increased* odds of pCI. The final model included an interaction between race and HADS-A (Supplementary Table 3). African American participants had on average higher HADS-A scores than Non-Hispanic White

Table 2 Agreement between self-report of cognitive difficulties and probable cognitive impairment assessed via Mini-Cog

		Self-Report of Confusion or Memory Loss in Previous 12 Months		Self-Report Cognitive Disorder	
		No	Yes	No	Yes
		1625 (78.9%)	435 (21.1%)	1981 (96.2%)	79 (3.8%)
Low Cognitive Risk (Mini-Cog 4–5)	1587 (77.0%)	1285 (62.4%)	302 (14.7%)	1543 (74.9.%)	44 (2.1%)
Probable Cognitive Impairment (Mini-Cog ≤ 3)	473 (23.0%)	340 (16.5%)	133 (6.5%)	438 (21.3%)	35 (1.7%)
Agreement between Mini-Cog and Self-Report		68.8%		76.6%	
Disagreement between Mini-Cog and Self-Report		31.2%		23.4%	
Adjusted McNemar's χ^2 Test		$p = 0.27$		$p < 0.001$	

Table 3 Final mixed effects logistic regression model with pCI as the dependent variable

Variable	Logistic Coefficient [95% CI]	Odds Ratio [95% CI]	*p*-value
Age*	0.41 [0.27,0.55]	1.51 [1.31,1.73]	< 0.001
Female *compared to* Male	-0.37 [-0.60,-0.13]	0.69 [0.55,0.88]	0.002
African American (AA) *compared to* Non-Hispanic White (NHW)	0.86 [0.55,1.17]	2.36 [1.74,3.21]	< 0.001
High School Graduate or GED *compared to* Not Completing High School	-0.37 [-0.76,0.02]	0.69 [0.47,1.03]	0.07
Some College or College Degree *compared to* Not Completing High School	-0.69 [-1.07,-0.31]	0.50 [0.34,0.73]	< 0.001
Body Mass Index (BMI)*	-0.13 [-0.26,-0.01]	0.88 [0.77,0.99]	0.04
Anxiety Symptoms (HADS-A)*	0.26 [0.11,0.41]	1.30 [1.12,1.51]	0.001
Interaction of Race (AA) and HADS-A	-0.27 [-0.49,-0.05]	0.76 [0.61,0.95]	0.02
Lung CT: Perc15*	0.14 [0.00,0.27]	1.14 [1.00,1.31]	0.046
Lung CT: Pi10*	0.22 [0.10,0.33]	1.24 [1.11,1.40]	< 0.001

Shown are variables significant at the $p<0.05$ level; Other candidate variables entered in the model that were removed by backward selection included: severe exacerbations in prior year, income, kidney disease, sleep apnea, coronary artery disease, peripheral vascular disease

Confidence Intervals (CI) were calculated using Wald Method

*Age, Perc15, Pi10, BMI, and HADS-A were standardized (centered on mean and divided by standard deviation)

participants. HADS-A was not associated with pCI in African Americans whereas higher anxiety was associated with pCI in Non-Hispanic White participants. Being female, Non-Hispanic White, having completed more education, and increased BMI were associated with *decreased* odds of pCI.

Post-hoc examination of lung CT measures by smoking/COPD group

Given that the frequency of pCI was elevated in PRISm and that higher (not lower as expected) Perc 15 was associated with pCI in our regression modeling, we conducted several post-hoc analyses to better understand Perc15 in relation to other variables in our sample and determine the potential impact of total lung volume and current smoking. First, we examined the pattern of standardized values for FEV1%predicted, Perc15 and Pi10 by smoking/COPD group (Supplemental Fig. 2 provides boxplots by group). The notable observation is that while Pi10 shows the anticipated pattern of increasing values from Never Smokers toward GOLD 4 (with PRISm similar to GOLD 2), the pattern for Perc15 differs. Perc15 is notably higher for PRISm than all other groups. Second, we re-analyzed the data utilizing adjusted lung density, which incorporates total lung volume, in place of Perc15 to determine whether differences in lung volume could account for the findings. The results were unchanged from the original model when using adjusted lung density (β =0.07, p = 0.05). Third, we considered the possibility that collinearity could be impacting our model; however, examining variance inflation factors showed that the model had no collinearity (max VIF=1.88 < 5) indicating that the inclusion of the two lung CT measures does not explain the observation. Finally, we examined the potential impact of current smoking as a main effect and interaction, and it did not change the direction of effect or statistical significance of Perc15.

Discussion

The goals of the study were to examine the prevalence of cognitive difficulties and identify clinical factors associated with probable cognitive impairment (pCI) in a large sample of older adults enriched for individuals with cigarette smoking exposure and COPD. 27% of participants with smoking exposure (≥ 10 pack-years) and evidence of lung disease on spirometry (PRISm or GOLD 1–4) had pCI based on the Mini-Cog, prevalence comparable to prior literature utilizing other dementia screening tools [2]. The highest frequencies of pCI were observed among individuals with PRISm physiology (reduced FEV_1 in the setting of a preserved FEV_1/FVC ratio) and very severe COPD (GOLD 4; both 30%). In contrast, 9% of never smokers and 19% of those with smoking exposure, but normal spirometry, had pCI. Regression modeling revealed that older age, male sex, African American race, lower education level, lower BMI, elevated anxiety, higher

lung density (Perc15) and more airway disease (Pi10) were associated with pCI. Evidence of a link between lung CT measures and pCI is an important contribution consistent with the idea that COPD-related lung pathophysiology may uniquely increase risk for cognitive impairment.

That individuals with COPD, classified using traditional GOLD criteria, are at higher risk for cognitive impairment than healthy age-matched controls has been demonstrated in multiple prior studies [59]; however, the observation that individuals with PRISm are at risk for cognitive impairment is not as well established. Individuals with PRISm have proportionate decreases in FEV_1 and FVC, a pattern associated with increased risk for mortality [60]. Participants in the Rotterdam study with PRISm or GOLD 2–4 were shown to have worse cognitive performance and a higher prevalence of vascular brain lesions than those with normal spirometry [61]. Kawatoko and colleagues [62] observed that community dwelling older adults with PRISm had a higher risk of new onset dementia in the subsequent 5 years than those with normal spirometry. PRISm may be an important clinical entity for identifying risk for cognitive impairment. Potential mechanisms by which PRISm may be linked to cognition include comorbid cardiovascular disease and systemic inflammation, which are common in PRISm [29, 63, 64] and known risk factors for cognitive impairment [65, 66].

The finding that COPD-related changes on lung CT improved predictions of pCI is important. Two previous studies have examined lung CT and cognition. One observed a link between the presence of emphysema, visually detected on CT, and worse cognition in midlife using data from community dwelling participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study [67]. Another examined a relatively smaller cohort of individuals diagnosed with COPD and concluded that emphysema was associated with cognitive impairment [68] In the COPDGene cohort higher Pi10, a measure of airway wall thickness was strongly associated with pCI. This suggests that airway disease may be an important aspect of COPD physiology increasing risk for cognitive impairment, perhaps through systemic inflammation and vascular mechanisms [69]. We anticipated that higher $LAA\text{-}856_E$, reflecting greater gas trapping, would be associated with pCI, but this association was not observed. Finally, contrary to our expectation, a significant association was observed between higher Perc15 and pCI. The presence of emphysema drives Perc15 lower and thus, we anticipated that lower, not higher, Perc15 would be associated with cognitive impairment. It is important to recognize that inflammation in the lung increases Perc15. Thus, it is possible that the association between higher Perc15 and pCI that we observed was due to lung inflammation. While we do not have direct measures of lung inflammation, in post-hoc analyses we observed that participants with PRISm showed increased Pi10 and also had higher Perc15 than any other group (Supplemental Fig. 2). The combined findings suggest that individuals with airway disease are at elevated risk for cognitive impairment. Airway disease could impact cognition via systemic inflammation and cardiovascular changes having downstream impact on the cerebrovasculature. It may be that the association between lung density measures and cognition differs across COPD progression with inflammation driving the association early. Taken together, the analyses suggest that altered lung physiology is associated with cognition beyond demographic and other clinical factors. Future studies should include lung CT measures and examine potential mechanisms driving the link with cognition, which may differ at different points in the progression of COPD.

In addition to pulmonary measures, several demographic and clinical characteristics were associated with pCI. Advanced age and lower education are known risk factors for cognitive impairment. The observation that male sex was associated with pCI could be due to higher rates of cardiovascular comorbidities and diabetes and is an area for future study [70]. pCI was more frequent among African Americans than non-Hispanic Whites in our sample. Previous studies in COPD have also observed elevated prevalence of cognitive impairment among African Americans [71]. Racial differences in risk are likely the result of health disparities such as environmental exposures, lifestyle factors, and access to medical treatment. Hence, clinicians should be aware of this risk and the importance of referral where appropriate.

The interaction between race and anxiety was statistically significant in the regression suggesting that anxiety was more strongly associated with pCI among non-Hispanic White participants than African American participants. African American participants overall (with or without PCI) had higher anxiety than non-Hispanic White participants (Supplementary Table 3). Given the smaller sample size for African American participants it is possible that we had limited power to detect an association between anxiety and pCI for this subset of participants. Clinically, it is essential to select screening tools that minimize bias from cultural differences. There is some evidence that the Mini-Cog shows less bias than some other screening tools [72], but careful consideration of individual clinical circumstances is essential including the possibility of a false positive result on screening measures associated with anxiety. Finally, lower BMI was associated with pCI. Low BMI may be a proxy for advanced COPD with associated cachexia [73] that may impact the brain and cognition.

The current analysis examined history of a cognitive disorder diagnosis and worsening confusion or memory loss. The contrast between the low number of participants who reported having a prior cognitive disorder diagnosis (4%) and the 27% identified as having pCI via the Mini-Cog may, in part, reflect the limitation of retrospective self-report, but is likely also driven by under-recognition of cognitive impairment [74, 75]. Recommendations for dementia screening include self-report and objective screening, as each provides unique information [38]. In our data, only 28% of the individuals who had pCI on the Mini-Cog reported worsening confusion or memory loss, suggesting that many participants that might benefit from further cognitive assessment would be missed using self-report alone. The discrepancy underscores the importance of a combination of a clinical interview and objective screening when identifying possible impairment.

Several study limitations are important to consider. First, the Mini-Cog is a screening tool and does not provide a diagnosis of cognitive impairment. Comprehensive cognitive disorder diagnosis was not conducted as a part of COPDGene. Nonetheless, the Mini-Cog has been validated in relation to gold-standard diagnosis [41] and is utilized clinically. Future work that includes comprehensive cognitive assessment is needed to confirm the results. Second, the assessment of medical comorbidities relied on self-report. Medical record review or diagnostic assessment would have yielded more precise information regarding comorbidities. Third, although we included 37 variables potentially relevant for cognition, there are other factors that may impact cognition that were not included. For example, limited data were available regarding developmental history and neuropsychiatric comorbidities. Additionally, other aspects of lung structure and function that can be identified using lung CT could be important such as interstitial lung abnormalities (ILA). Finally, the way in which participants were recruited for COPDGene impacts the population of people that our results are likely to generalize to. COPDGene included only a small number of individuals who were never smokers and thus, it is not optimally designed for examining the effect of cigarette smoking exposure compared to never smoking on cognition. While we did include initial descriptive comparisons that included never smokers, the primary modeling and conclusions are not focused on presence or absence of smoking per se, but rather characteristics associated with cognitive impairment among individuals enriched for those with a significant cigarette smoking history. Related to the structure of the cohort, COPDGene did not recruit individuals with COPD in the absence of cigarette smoking history and thus, we cannot be sure that our conclusions generalize to individuals with COPD who have not previously smoked cigarettes. Despite these limitations, the present study included a large sample of individuals well-characterized regarding pulmonary function and, importantly, included people with smoking exposure regardless of COPD diagnosis capturing the full spectrum of COPD including those with PRISm, representing a strength.

Conclusions

In summary, older adults with a history of smoking exposure had elevated prevalence of pCI assessed via the Mini-Cog, particularly those with PRISm and very severe COPD (GOLD 4). Higher Perc15 and Pi10 were associated with pCI after accounting for a broad set of demographic and clinical variables. Lung CT may identify underlying pathophysiology that has downstream impacts on the brain. Further research replicating these findings and examining the possibility that the predominant mechanisms impacting cognition may differ among people with different COPD-related phenotypes will be important to build upon the findings. The current analyses highlight the importance of focusing on individuals with airway predominant disease and PRISm. Given heterogeneity within PRISm it is likely that there are certain individuals who are at particularly enhanced risk for cognitive impairment.

Abbreviations

COPD	Chronic Obstructive Pulmonary Disease
pCI	Probable Cognitive Impairment
CT	Computed Tomography
GOLD	Global Initiative for Chronic Obstructive Lung Disease
PRISm	Preserved Ratio Impaired Spirometry
COPDGene	COPD Genetic Epidemiology study
Perc15	Lung density at the 15th percentile of the lung density histogram
Pi10	Average wall thickness of a theoretical airway with a lumen perimeter of 10 mm
MCI	Mild Cognitive Impairment
SpO_2	Blood oxygen saturation
DLCO	Diffusion capacity for carbon monoxide
Kg	Kilograms
M	Meters
BMI	Body Mass Index
DASI	Duke Activity Status Index
HADS-A	Hospital Anxiety and Depression Scale- Anxiety Subscale
HADS-D	Hospital Anxiety and Depression Scale- Depression Subscale
mMRC	Modified Medical Research Council dyspnea scale
CAT	COPD Assessment Test
MSv	Millisieverts
HU	Hounsfield Units
LAA	Low Attenuation Area
FEV1	Forced Expiratory Volume in 1 s
FVC	Forced Vital Capacity
mm	Millimeters
MGM	Mixed Graphical Model
PVD	Peripheral Vascular Disease
CAD	Coronary Artery Disease
VIF	Variance Inflation Factor

Supplementary Information

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Supplementary Material 1: Supplementary Table 1. Frequencies of history of cognitive concerns and probable cognitive impairment based on the Mini-Cog. Supplementary Table 2. Frequencies of Mini-Cog Clock Drawing Error Types by Smoking/COPD Group. Supplementary Table 3. Interaction of Race x HADS-A. Supplementary Figure 1. Mixed graphical model for demographic and clinical variables and probable cognitive impairment (pCI) defined by Mini-Cog ≤3 (diamond node labeled '1'). Lines or edges connecting nodes show a dependency between two variables, conditional because it is the relationship after adjusting for all other variables and their pairwise interactions. The strongest 50% of the pair-wise relationships in the network are plotted with edges connecting the nodes. Thicker lines correspond to stronger dependencies. Dark grey edges connect pCI to the candidate variables and the lighter orange color depict edges between two non-Mini-Cog variables. Supplementary Figure 2. Side-by-side boxplots of smoking/COPD group by three standardized clinical variables: FEV1pp (left panel), Perc15 (center panel), and Pi10 (right panel). Values were standardized to facilitate comparison across measures.

Supplementary Material 2: Appendix A. COPDGene Sites and Investigators. Appendix B. COPDGene Phase 3 Mini-Cog Clock Drawing Error Classification.

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Authors' contributions
JDN, EAR, BM, APC, EAH, SF, DLD, ASI, MGF, SPB, KMK, EKS, and JDC contributed to study data collection. KFH, CL, EAR, and BM developed cognitive data processing procedures. KFH conceived of the current work with GLK and EA contributing to study design. EA implemented the statistical analysis. CL, GLK, JDN, KAP, APC, JGF, AMY, KFP, and SML contributed to the interpretation of data. KFH, CL, and EA drafted the initial version of the manuscript, and all authors provided input on subsequent revisions and approved the submitted version.

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Data availability
Data for the COPDGene study are deposited in dbGAP. The specific combination of data analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki. The study was approved by each center's Institutional Review Board (see list of centers in Appendix A) and written documentation of the informed consent process was provided by all participants.

Consent for publication
Not applicable.

Competing interests
JDN is a paid consultant, Medical Advisor, holder of stock shares and stock options with VIDA Diagnostics. JDN shares patents with VIDA Diagnostics and the University of Iowa. JDN receives Royalties from Elsevier and is a paid advisor to Sanofi. BM reports royalties from Wolters Kluwer Health, consulting fees from AstraZeneca, honoraria from Regeneron, and participation on advisory boards for Sanofi, Verona, Regeneron, GSK, Mt. Sinai, Baystate Medical Center and AstraZeneca. EAH reports consulting fees from Sanofi and that he is a founder and shareholder for VIDA Diagnostics. SF owns stock in ROMTech. DLD reports grant support from Bayer and the Alpha-1 Foundation and reports funds from Astra Zeneca as a member of a Medical Advisory Board. AMY reports consulting fees from Cheisi Bio Pharma and travel fees from Theravance Bio Pharma Limited. AMY is Associate Editor of Respiratory Medicine; his participation on the project complies with Respiratory Medicine requirements for recusal from review and decisions for submitted manuscript. ASI reports consulting fees from consulting fees from Verona, AstraZeneca and Medscape. MGF reports grant support from Novartis Beacon of Hope Center of Excellence. SPB reports grant funding from AstraZeneca, Connect Biopharma, Apreo, Sanofi, Genentech, Nuyaira, and the COPD Foundation, royalties from Springer, consulting fees from Sanofi, Regeneron, Chiesi, GSK, Genentech, Connect Biopharma, Apreo, Merck, AstraZeneca, Kymera, Verona, Boehringer Ingelheim, Uniquity, Polarean, and payments or honoraria from Medscape, Horizon CME, Integrity CE, Illuminate Health, and Integritas Communications. KMK reports payment from Nuvaira for participation on a data and safety monitoring board and travel support from Gilead Sciences. EKS reports grant support from Bayer and Northpond Laboratories. JC and DLD are on the COPD Foundation Board of Directors. KFH, BM, and DLD are members of the COPD Foundation Medical and Scientific Advisory Board. CL, APC, EAR, JGF, GLK, SML, KAP, and EA declare that they have no competing interests.

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