

Supplemental Online Data for:
The presence of emphysema on chest imaging and mid-life cognition

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(computed tomography) visual emphysema stratified by pack years (0 pack years, >0-10 pack years, and >10 pack years). Shown for each cognitive test is the multivariable linear regression beta coefficient (95% confidence interval) for the association between emphysema and cognitive test z-score. Negative values reflect worse cognitive test performance, where -1.0 is a 1 standard deviation worse test score and +1.0 is a 1 standard deviation better test score.

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Full description of research methods:

Study design, setting, and participants

CARDIA (Coronary Artery Risk Development in Young Adults) is a prospective cohort study that enrolled 5,115 black and white participants aged 18-30 years old in 1985-1986 from communities in Birmingham, AL, Chicago, IL, Minneapolis, MN, and Oakland, CA (E1). Follow up visits were conducted at year 2, 5, 7, 10, 15, 20, 25, and 30. Chest computed tomography (CT) scans were obtained in year 25 and a cognitive assessment was conducted in year 30. The study was approved by institutional review boards at each center. Written informed consent was obtained from all participants.

Chest CT emphysema

At study year 25, all participants had chest CT scans obtained and visual assessment of emphysema was performed using methods previously described (E2-5). Three trained radiologists analyzed the chest CT images for the presence or absence of visual emphysema. Reader 1 reviewed all the CT scans and categorized them as having centrilobular emphysema, paraseptal emphysema, or neither. Reader 2 then reviewed all images that were categorized as having visual emphysema (centrilobular emphysema, paraseptal emphysema, or both) plus an additional random 10% sample of the remaining images. A third reader adjudicated the images in which there was disagreement between readers 1 and 2. The Kappa agreement between readers 1 and 2 for centrilobular emphysema was 0.74 and for paraseptal emphysema was 0.70. There were no cases of panlobular emphysema identified on visual assessment.

Cognitive assessments

At year 30, participants completed cognitive tests including the Montreal Cognitive Assessment (MoCA), the Rey Auditory Verbal Learning Test (RAVLT), the Digit Symbol Substitution Test (DSST), the Stroop Test, and tests of verbal fluency (category fluency and letter fluency).

The MoCA was designed as a rapid screening instrument for mild cognitive impairment and has been validated in 55 to 85 year-old adults (E6). Using a series of activities and questions, the test assesses different cognitive domains including attention and concentration, executive function, memory, language, visuospatial skills, conceptual thinking, calculations, and orientation. The MoCA can be administered by anyone who understands and follows the test instructions but requires a trained health professional for interpretation. Total time to administer the MoCA is approximately 10 minutes and the results are scored on a scale of 1-30. Scores less than 26 indicate mild cognitive impairment with a sensitivity of 90% and specificity of 87%.

The RAVLT is a test of verbal memory and measures ability to encode, consolidate, store and retrieve verbal information (E7). Individuals are given a list of 15 unrelated words (list A) and asked to repeat all the words they remember. This is repeated for 5 trials. The individual is then presented with a second list of 15 unrelated words (list B) and asked to repeat as many words as they can remember. The second list of words is

used only for 1 trial. The individual is then asked to recall as many words from the first list of unrelated words (list A). After a delay of approximately 10 minutes, the individual is again asked to recall as many of the first list of words (list A) as they can remember. Delayed recall scores were used for the analysis.

The DSST test is a part of the larger Weschler Adult Intelligence Test (E8). It is a high sensitivity pencil and paper test that assesses mainly attention, working memory, and psychomotor speed. Individuals are presented with a key consisting of numbers 1-9 that are paired with symbols. The individual is then given 120 seconds to use the key to write matching symbols by a series of numbers in a grid. The score is determined by the number of correct number-symbol matches completed and higher scores indicate better performance. Credit is not given for items completed out of sequence and the maximum score is 133.

The Stroop Test measures executive function, attention, processing speed, cognitive flexibility, and working memory (E9). It is composed of three components (word pages, color pages, and word-color pages). Each of the three components require individuals to identify as many objects as possible within 120 seconds. In the first part, individuals read the names of colors printed in black ink. In the second part, individuals name colored rectangles in green, blue, yellow, or red ink. In the last part, individuals are shown names of colors in different colored ink and asked to name the color of the ink (not the written color). Each of the three subtests are scored based on time to completion in seconds and number correct out of 40. An inference score was calculated by taking the subtest 3 time to completion plus the number incorrect minus subtest 2 time to completion plus the number incorrect. The interference score was used for the analysis. In contrast to other cognitive tests where higher scores indicate better performance, lower scores indicate better performance on the Stroop interference score. We therefore presented the inverse of the interference score for clarity and consistency of presentation.

Verbal fluency testing measures verbal ability and executive control (E10). It consists of two tasks: category fluency (semantic fluency) and letter fluency (phonemic fluency). The category fluency test consists of a participant naming as many animals as possible in 60 seconds. Higher scores indicate better performance. In the letter fluency test, participants were given the letter 'A' and then the letter 'S' of the alphabet and asked to list as many words that start with the specified letter in 60 seconds.

Spirometry

Lung function was measured at years 0, 2, 5, 10, 20, and 30. At all examinations, pre-bronchodilator spirometry was performed in accordance with procedures recommended by the American Thoracic Society (E11-14). Peak forced expiratory volume in 1 second (FEV₁) was defined as the highest FEV₁ recorded over the 30-year study period. Annualized FEV₁ decline was calculated by subtracting the year 5 FEV₁ from year 30 FEV₁ and dividing by 25.

Physical activity

The CARDIA Physical Activity Questionnaire was designed to collect information about a participant's usual activity patterns by self-report of activities in the previous 12 months. It has been validated to assess leisure and work time physical activity. Participants are asked about a series of different activities and the frequency and intensity of each. Activities are defined as vigorous intensity if they cause increased heart rate, increased body temperature, sweating, or hard breathing. A composite score is generated that takes into account both the intensity and frequency of all activities. Sub-scores for moderate and heavy intensity activities are also calculated. The scores from total physical activity were used in the analysis.

Statistical Analysis

Participants were excluded if they were missing chest CT or spirometry data, or if they were missing more than two cognitive function scores.

Multivariable linear regression was used to determine the association between visual emphysema on chest CT imaging and cognitive dysfunction. Model covariates included age, sex, race, study center, height, body mass index (BMI), years of education, smoking status (current, former, and never), smoking pack years at year 25, and cigarettes per day among current and former smokers. Additional multivariable linear regression models adjusting for each FEV₁, peak FEV₁, and annualized FEV₁ decline were developed to assess the association between visual emphysema and cognitive dysfunction independent of spirometry. To further explore effects on global cognitive function measured by the MoCA, a multivariable logistic regression model was used. We also conducted analyses stratified by smoking status (current, former, and never) and pack years (>10 pack years, >0-10 pack years, and 0 pack years).

We also conducted a post-hoc mediator analysis to explore potential mechanisms that might mediate the association between emphysema and cognition. These variables were chosen since they were collected in the complete cohort. Mediation models were developed using the "Mediation" package in R software. For models testing the association between emphysema and cognition, we analyzed mediation by emphysema-induced systemic inflammation by inserting Year 25 plasma C-reactive protein (CRP) as mediator. We also explored physical activity as a mediator of the association between emphysema and cognition. Here, we inserted the Year 25 total activity scores derived from the CARDIA Physical Activity Questionnaire as mediators.

Analyses were conducted using SAS 14.1 (Cary, NC, USA) and R 4.0.0 (R Core Team, 2020).

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e-Table 1: Differences in cognitive test z-scores between CARDIA (Coronary Artery Risk Development in Young Adults) cohort participants with and without chest CT (computed tomography) visual emphysema. Shown for each cognitive test is the multivariable linear regression beta coefficient (95% confidence interval) for the association between emphysema and cognitive test z-score. Negative values reflect worse cognitive test performance, where -1.0 is a 1 standard deviation worse test score and +1.0 is a 1 standard deviation better test score.

Cognitive Assessment	Chest CT Visual Emphysema and Year 30 Cognitive Assessment									
	Unadjusted		Model 1		Model 2		Model 3		Model 4	
	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95%CI)	<i>P</i>
MoCA	-0.84 (-0.99 to -0.69)	<0.01	-0.39 (-0.53 to -0.25)	<0.01	-0.36 (-0.50 to -0.22)	<0.01	-0.38 (-0.52 to -0.24)	<0.01	-0.30 (-0.45 to -0.16)	<0.01
RAVLT	-0.67 (-0.83 to -0.53)	<0.01	-0.27 (-0.42 to -0.12)	<0.01	-0.25 (-0.40 to -0.10)	<0.01	-0.27 (-0.42 to -0.12)	<0.01	-0.24 (-0.39 to -0.08)	<0.01
DSST	-0.79 (-0.95 to -0.64)	<0.01	-0.29 (-0.43 to -0.14)	<0.01	-0.26 (-0.40 to -0.11)	<0.01	-0.28 (-0.42 to -0.14)	<0.01	-0.23 (-0.38 to -0.08)	<0.01
Letter Fluency	-0.52 (-0.68 to -0.36)	<0.01	-0.25 (-0.42 to -0.09)	<0.01	-0.23 (-0.40 to -0.07)	<0.01	-0.25 (-0.41 to -0.08)	<0.01	-0.22 (-0.39 to -0.04)	0.014
Stroop*	-0.48 (-0.64 to -0.33)	<0.01	-0.12 (-0.29 to 0.04)	0.13	-0.11 (-0.27 to 0.05)	0.18	-0.12 (-0.28 to 0.04)	0.150	-0.11 (-0.28 to 0.06)	0.217
Category Fluency	-0.38 (-0.53 to -0.22)	<0.01	-0.08 (-0.23 to 0.08)	0.35	-0.06 (-0.22 to 0.09)	0.43	-0.07 (-0.23 to 0.09)	0.367	-0.03 (-0.20 to 0.14)	0.725

Model 1 covariates: age, sex, race, BMI, height, study center, education, cigarettes per day, and pack-years of smoking

Model 2 covariates: model 1 + year 30 maximum FEV₁

Model 3 covariates: model 1 + peak FEV₁ over 30 years

Model 4 covariates: model 1 + annualized FEV₁ decline

*Stroop interference scores have been reported as an inverse score for consistency with other tests. In contrast to other cognitive tests, higher raw Stroop scores reflect worse cognitive performance

Definition of abbreviations: BMI = body mass index; CI = confidence interval; DSST = Digit Symbol Substitution Test; FEV₁ = forced expiratory volume in one second; MoCA = Montreal Cognitive Assessment; RAVLT = Long Delay Rey Auditory Verbal Learning Test; Stroop = Stroop Test.

e-Table 2: Odds (95% confidence intervals) of having an abnormal Montreal Cognitive Assessment score of <26 in the presence of chest CT (computed tomography) visual emphysema.

	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
MoCA <26	4.54 (2.92 to 7.03)	2.47 (1.48 to 4.11)	2.35 (1.41 to 3.92)	2.45 (1.47 to 4.07)	2.45 (1.45 to 4.16)

Model 1 covariates: age, sex, race, BMI, height, study center, education, cigarettes per day, and pack years

Model 2 covariates: model 1 + year 30 maximum FEV₁

Model 3 covariates: model 1 + peak FEV₁ over 30 years

Model 4 covariates: model 1 + annualized FEV₁ decline

Definition of abbreviations: BMI = body mass index; CI = confidence interval; FEV₁ = forced expiratory volume in one second; MoCA = Montreal Cognitive Assessment; OR = odds ratio.

e-Table 3: Differences in cognitive test z-scores between CARDIA (Coronary Artery Risk Development in Young Adults) cohort participants with and without chest CT (computed tomography) visual centrilobular emphysema and paraseptal emphysema. Shown for each cognitive test is the multivariable linear regression beta coefficient (95% confidence interval) for the association between emphysema and cognitive test z-score. Negative values reflect worse cognitive test performance, where -1.0 is a 1 standard deviation worse test score and +1.0 is a 1 standard deviation better test score.

Cognitive Assessment	Chest CT Visual Emphysema and Year 30 Cognitive Assessment									
	Unadjusted		Model 1		Model 2		Model 3		Model 4	
	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95%CI)	<i>P</i>
Centrilobular Emphysema (n=106)										
MoCA	-0.49 (-0.72 to -0.27)	<0.01	-0.27 (-0.46 to -0.08)	<0.01	-0.25 (-0.44 to -0.06)	0.01	-0.27 (-0.46 to -0.08)	<0.01	-0.18 (-0.38 to 0.02)	0.07
RAVLT	-0.42 (-0.64 to -0.19)	<0.01	-0.28 (-0.49 to -0.08)	<0.01	-0.27 (-0.47 to -0.06)	0.01	-0.28 (-0.49 to -0.08)	<0.01	-0.27 (-0.48 to -0.05)	0.01
DSST	-0.39 (-0.61 to -0.16)	<0.01	-0.17 (-0.36 to 0.02)	0.09	-0.15 (-0.34 to 0.05)	0.14	-0.17 (-0.36 to 0.03)	0.09	-0.13 (-0.34 to 0.07)	0.2
Letter Fluency	-0.39 (-0.63 to -0.16)	<0.01	-0.26 (-0.47 to -0.04)	0.02	-0.24 (-0.46 to 0.02)	0.03	-0.25 (-0.47 to -0.03)	0.02	-0.22 (-0.45 to 0.01)	0.07
Stroop*	-0.14 (-0.37 to 0.09)	0.22	0.02 (-0.20 to 0.24)	0.85	0.03 (-0.18 to 0.25)	0.77	0.02 (-0.19 to 0.24)	0.84	0.05 (-0.18 to 0.28)	0.67
Category Fluency	-0.18 (-0.41 to 0.05)	0.12	-0.03 (-0.25 to 0.18)	0.77	-0.02 (-0.24 to 0.19)	0.82	-0.03 (-0.25 to 0.18)	0.77	-0.01 (-0.24 to 0.21)	0.91
Paraseptal Emphysema (n=131)										
MoCA	-0.64 (-0.84 to -0.43)	<0.01	-0.25 (-0.42 to -0.07)	<0.01	-0.23 (-0.41 to -0.06)	0.01	-0.24 (-0.42 to -0.07)	<0.01	-0.16 (-0.34 to 0.02)	0.08
RAVLT	-0.52 (-0.72 to -0.32)	<0.01	-0.12 (-0.31 to 0.07)	0.20	-0.11 (-0.30 to 0.08)	0.26	-0.12 (-0.31 to 0.07)	0.21	-0.09 (-0.28 to 0.10)	0.36
DSST	-0.68 (-0.88 to -0.48)	<0.01	-0.22 (-0.40 to -0.04)	0.02	-0.20 (-0.38 to -0.03)	0.03	-0.22 (-0.39 to -0.04)	0.02	-0.15 (-0.34 to 0.03)	0.11
Letter Fluency	-0.34 (-0.56 to -0.13)	<0.01	-0.12 (-0.33 to 0.08)	0.25	-0.11 (-0.31 to 0.10)	0.30	-0.12 (-0.32 to 0.09)	0.26	-0.09 (-0.30 to 0.12)	0.42
Stroop*	-0.49 (-0.70 to -0.28)	<0.01	-0.17 (-0.37 to 0.03)	0.10	-0.16 (-0.36 to 0.04)	0.11	-0.17 (-0.37 to 0.03)	0.10	-0.15 (-0.36 to 0.06)	0.15
Category Fluency	-0.37 (-0.58 to -0.16)	<0.01	-0.11 (-0.30 to 0.09)	0.28	-0.10 (-0.30 to 0.10)	0.31	-0.11 (-0.30 to 0.09)	0.29	-0.04 (-0.24 to 0.17)	0.73

Model 1 covariates: age, sex, race, BMI, height, study center, education, cigarettes per day, and pack-years of smoking

Model 2 covariates: model 1 + year 30 maximum FEV₁

Model 3 covariates: model 1 + peak FEV₁ over 30 years

Model 4 covariates: model 1 + annualized FEV₁ decline

*Stroop interference scores have been reported as an inverse score for consistency with other tests. In contrast to other cognitive tests, higher raw Stroop scores reflect worse cognitive performance

Definition of abbreviations: BMI = body mass index; CI = confidence interval; DSST = Digit Symbol Substitution Test; FEV₁ = forced expiratory volume in one second; MoCA = Montreal Cognitive Assessment; RAVLT = Long Delay Rey Auditory Verbal Learning Test; Stroop = Stroop Test.

e-Table 4: Differences in cognitive test z-scores between CARDIA (Coronary Artery Risk Development in Young Adults) cohort participants with and without chest CT (computed tomography) visual emphysema, stratified by smoking status (current, former, and never). Shown for each cognitive test is the multivariable linear regression beta coefficient (95% confidence interval) for the association between emphysema and cognitive test z-score. Negative values reflect worse cognitive test performance, where -1.0 is a 1 standard deviation worse test score and +1.0 is a 1 standard deviation better test score.

Cognitive Assessment	Chest CT Visual Emphysema and Year 30 Cognitive Assessment							
	Model 1		Model 2		Model 3		Model 4	
	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>
Current Smoker (n=372)								
MoCA	-0.16 (-0.39 to 0.06)	0.16	-0.16 (-0.39 to 0.07)	0.17	-0.16 (-0.38 to 0.07)	0.17	-0.02 (-0.25 to 0.20)	0.85
RAVLT	-0.08 (-0.30 to 0.14)	0.50	-0.06 (-0.28 to 0.16)	0.57	-0.08 (-0.30 to 0.14)	0.49	0.02 (-0.21 to 0.25)	0.84
DSST	-0.10 (-0.32 to 0.11)	0.33	-0.09 (-0.30 to 0.12)	0.40	-0.10 (-0.32 to 0.11)	0.33	-0.02 (-0.24 to 0.21)	0.90
Letter Fluency	0.05 (-0.19 to 0.29)	0.69	0.05 (-0.19 to 0.30)	0.67	0.05 (-0.19 to 0.29)	0.69	0.11 (-0.15 to 0.37)	0.42
Stroop*	0.08 (-0.22 to 0.37)	0.62	0.09 (-0.21 to 0.39)	0.56	0.08 (-0.21 to 0.38)	0.59	0.09 (-0.23 to 0.42)	0.58
Category Fluency	0.06 (-0.16 to 0.29)	0.59	0.08 (-0.15 to 0.30)	0.51	0.06 (-0.16 to 0.29)	0.58	0.14 (-0.10 to 0.37)	0.27
Former Smoker (n=551)								
MoCA	-0.53 (-0.81 to -0.26)	<0.01	-0.49 (-0.76 to -0.21)	<0.01	-0.53 (-0.80 to -0.25)	<0.01	-0.48 (-0.76 to -0.20)	<0.01
RAVLT	-0.34 (-0.65 to -0.03)	0.03	-0.33 (-0.65 to -0.01)	0.04	-0.34 (-0.65 to -0.03)	0.03	-0.38 (-0.70 to -0.06)	0.02
DSST	-0.32 (-0.61 to -0.04)	0.03	-0.32 (-0.61 to -0.03)	0.03	-0.33 (-0.62 to -0.04)	0.03	-0.30 (-0.59 to -0.00)	0.05
Letter Fluency	-0.54 (-0.87 to -0.20)	<0.01	-0.53 (-0.87 to -0.20)	<0.01	-0.54 (-0.88 to -0.21)	<0.01	-0.56 (-0.91 to -0.21)	<0.01
Stroop*	-0.28 (-0.55 to -0.01)	0.05	-0.25 (-0.52 to 0.03)	0.08	-0.27 (-0.54 to 0.01)	0.06	-0.27 (-0.54 to 0.01)	0.06
Category Fluency	-0.35 (-0.68 to -0.02)	0.04	-0.40 (-0.73 to -0.06)	0.02	-0.37 (-0.70 to -0.04)	0.03	-0.34 (-0.68 to 0.00)	0.05
Never Smoker (n=1568)								
MoCA	-0.61 (-0.93 to -0.30)	<0.01	-0.56 (-0.88 to -0.25)	<0.01	-0.60 (-0.91 to -0.29)	<0.01	-0.63 (-0.95 to -0.30)	<0.01
RAVLT	-0.51 (-0.84 to -0.17)	<0.01	-0.47 (-0.80 to -0.13)	<0.01	-0.50 (-0.84 to -0.17)	<0.01	-0.53 (-0.88 to -0.18)	<0.01
DSST	-0.59 (-0.91 to -0.27)	<0.01	-0.53 (-0.85 to -0.21)	<0.01	-0.58 (-0.90 to -0.26)	<0.01	-0.58 (-0.91 to -0.24)	<0.01
Letter Fluency	-0.53 (-0.90 to -0.17)	<0.01	-0.49 (-0.85 to -0.13)	<0.01	-0.53 (-0.89 to -0.16)	<0.01	-0.52 (-0.89 to -0.14)	<0.01
Stroop*	-0.28 (-0.63 to 0.07)	0.12	-0.27 (-0.62 to 0.08)	0.13	0.28 (-0.63 to 0.07)	0.12	-0.26 (-0.63 to 0.11)	0.17
Category Fluency	-0.12 (-0.47 to 0.23)	0.51	-0.08 (-0.43 to 0.27)	0.65	0.11 (-0.46 to 0.24)	0.54	-0.06 (-0.43 to 0.31)	0.75

Model 1 covariates: age, sex, race, BMI, height, study center, education, cigarettes per day, and pack-years of smoking

Model 2 covariates: model 1 + year 30 maximum FEV₁

Model 3 covariates: model 1 + peak FEV₁ over 30 years

Model 4 covariates: model 1 + annualized FEV₁ decline

*Stroop interference scores have been reported as an inverse score for consistency with other tests. In contrast to other cognitive tests, higher Stroop scores reflect worse cognitive performance.

Definition of abbreviations: BMI = body mass index; CI = confidence interval; DSST = Digit Symbol Substitution Test; FEV₁ = forced expiratory volume in one second; MoCA = Montreal Cognitive Assessment; RAVLT = Long Delay Rey Auditory Verbal Learning Test; Stroop = Stroop Test.

e-Table 5: Differences in cognitive test z-scores between CARDIA (Coronary Artery Risk Development in Young Adults) cohort participants with and without chest CT (computed tomography) visual emphysema stratified by pack-years of smoking (>10 pack-years, >0-10 pack-years, and 0 pack-years). Shown for each cognitive test is the multivariable linear regression beta coefficient (95% confidence interval) for the association between emphysema and cognitive test z-score. Negative values reflect worse cognitive test performance, where -1.0 is a 1 standard deviation worse test score and +1.0 is a 1 standard deviation better test score.

Cognitive Assessment	Chest CT Visual Emphysema and Year 30 Cognitive Assessment							
	Model 1		Model 2		Model 3		Model 4	
	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>	β coefficient (95% CI)	<i>P</i>
>10 pack years (n=470)								
MoCA	-0.28 (-0.46 to -0.10)	<0.01	-0.26 (-0.44 to -0.07)	<0.01	-0.27 (-0.45 to -0.08)	<0.01	-0.23 (-0.42 to -0.04)	0.02
RAVLT	-0.18 (-0.38 to 0.02)	0.08	-0.16 (-0.36 to 0.04)	0.12	-0.18 (-0.38 to 0.02)	0.08	-0.11 (-0.32 to 0.10)	0.29
DSST	-0.19 (-0.38 to -0.01)	0.04	-0.16 (-0.35 to 0.02)	0.08	-0.19 (-0.37 to -0.00)	0.05	-0.15 (-0.35 to 0.05)	0.13
Letter Fluency	-0.24 (-0.45 to -0.03)	0.03	-0.24 (-0.45 to -0.03)	0.03	-0.24 (-0.45 to -0.02)	0.03	-0.25 (-0.48 to -0.03)	0.03
Stroop*	-0.14 (-0.37 to 0.09)	0.23	-0.13 (-0.36 to 0.10)	0.28	-0.13 (-0.36 to 0.10)	0.27	-0.14 (-0.39 to 0.11)	0.26
Category Fluency	-0.03 (-0.23 to 0.18)	0.80	-0.01 (-0.22 to 0.20)	0.91	-0.03 (-0.23 to 0.18)	0.81	0.01 (-0.22 to 0.23)	0.96
>0-10 pack years (n=579)								
MoCA	-0.45 (-0.79 to -0.11)	<0.01	-0.43 (-0.77 to -0.09)	0.01	-0.45 (-0.79 to -0.11)	<0.01	-0.12 (-0.48 to 0.23)	0.50
RAVLT	-0.21 (-0.56 to 0.13)	0.23	-0.19 (-0.54 to 0.15)	0.28	-0.21 (-0.56 to 0.13)	0.23	-0.15 (-0.52 to 0.22)	0.42
DSST	-0.35 (-0.68 to -0.03)	0.03	-0.34 (-0.67 to -0.02)	0.04	-0.35 (-0.68 to -0.03)	0.03	-0.17 (-0.51 to 0.18)	0.35
Letter Fluency	-0.02 (-0.40 to 0.37)	0.93	-0.01 (-0.40 to 0.37)	0.96	-0.02 (-0.40 to 0.37)	0.94	0.22 (-0.20 to 0.64)	0.31
Stroop*	-0.08 (-0.47 to 0.30)	0.67	-0.04 (-0.42 to 0.34)	0.84	-0.08 (-0.46 to 0.30)	0.69	-0.04 (-0.44 to 0.36)	0.84
Category Fluency	-0.21 (-0.57 to 0.16)	0.26	-0.22 (-0.59 to 0.14)	0.23	-0.21 (-0.57 to 0.16)	0.26	-0.05 (-0.44 to 0.34)	0.81
0 pack years (n=1568)								
MoCA	-0.58 (-0.95 to -0.21)	<0.01	-0.53 (-0.90 to -0.16)	<0.01	-0.57 (-0.94 to -0.20)	<0.01	-0.60 (-0.97 to -0.24)	<0.01
RAVLT	-0.50 (-0.90 to -0.10)	0.01	-0.47 (-0.87 to -0.06)	0.02	-0.50 (-0.90 to -0.09)	0.02	-0.50 (-0.90 to -0.10)	0.01
DSST	-0.41 (-0.79 to -0.02)	0.04	-0.35 (-0.73 to 0.03)	0.07	-0.39 (-0.77 to -0.01)	0.05	-0.40 (-0.78 to -0.01)	0.04
Letter Fluency	-0.52 (-0.95 to -0.10)	0.02	-0.47 (-0.90 to -0.04)	0.03	-0.51 (-0.94 to -0.08)	0.02	-0.51 (-0.94 to -0.08)	0.02
Stroop*	-0.06 (-0.47 to 0.35)	0.79	-0.06 (-0.47 to 0.35)	0.77	-0.06 (-0.47 to 0.35)	0.77	-0.04 (-0.45 to 0.38)	0.86
Category Fluency	0.01 (-0.42 to 0.43)	0.97	0.05 (-0.38 to 0.47)	0.83	0.02 (-0.40 to 0.44)	0.93	0.01 (-0.41 to 0.44)	0.95

Model 1 covariates: age, sex, race, BMI, height, study center, education, and pack-years of smoking in the >10 and 0-10 pack-year groups only

Model 2 covariates: model 1 + year 30 maximum FEV₁

Model 3 covariates: model 1 + peak FEV₁ over 30 years

Model 4 covariates: model 1 + annualized FEV₁ decline

*Stroop interference scores have been reported as an inverse score for consistency with other tests. In contrast to other cognitive tests, higher Stroop scores reflect worse cognitive performance.

Definition of abbreviations: BMI = body mass index; CI = confidence interval; DSST = Digit Symbol Substitution Test; FEV₁ = forced expiratory volume in one second; MoCA = Montreal Cognitive Assessment; RAVLT = Long Delay Rey Auditory Verbal Learning Test; Stroop = Stroop Test.

e-Table 6: Analysis of mediation effects of Year 25 plasma C-reactive protein (CRP) on the association between emphysema and cognition. Effects represent the point estimates (95% confidence interval) of the direct effects, indirect effects, and percent mediated of CRP on the model.

Cognitive Assessment	Direct Effect (95% CI)	Indirect Effect (95% CI)	Percent Mediated (95% CI); <i>P</i> -value
MoCA	-1.479 (-2.10 to -0.86)	-0.016 (-0.06 to 0.02)	0.9 (-1.0 to 4.0) <i>P</i> =0.30
RAVLT	-0.893 (-1.40 to -0.35)	-0.016 (-0.05 to 0.01)	1.6 (-1.7 to 8.0) <i>P</i> =0.25
DSST	-4.473 (-6.76 to -2.09)	-0.207 (-0.44 to -0.04)	4.3 (0.7 to 12.0) <i>P</i> =0.01
Letter Fluency	-3.185 (-5.35 to -0.98)	-0.068 (-0.24 to 0.06)	1.8 (-2.2 to 10.0) <i>P</i> =0.31
Stroop	1.497 (-0.42 to 3.48)	-0.013 (-0.16 to 0.11)	-0.6 (-23.5 to 18.0) <i>P</i> =0.86
Category Fluency	-0.439 (-1.27 to 0.42)	-0.015 (-0.07 to 0.03)	1.7 (-34.6 to 34.0) <i>P</i> =0.66

Definition of abbreviations: CI = Confidence Interval; DSST = Digit Symbol Substitution Test; MoCA = Montreal Cognitive Assessment; RAVLT = Rey Auditory Verbal Learning Test; Stroop = Stroop Test.

e-Table 7: Analysis of mediation effects of Year 25 total physical activity on the association between emphysema and cognition. Effects represent the point estimates (95% confidence interval) of the direct effects, indirect effects, and percent mediated of total physical activity on the model.

Cognitive Assessment	Direct Effect (95% CI)	Indirect Effect (95% CI)	Percent Mediated (95% CI); <i>P</i> -value
MoCA	-1.500 (-2.12 to -0.88)	0.005 (-0.01 to 0.03)	-0.2 (-2.3 to 1.0) <i>P</i> =0.59
RAVLT	-0.904 (-1.40 to -0.36)	0.006 (-0.30 to 0.01)	0.3 (-1.28 to 4.0) <i>P</i> =0.61
DSST	-4.746 (-7.01 to -2.39)	0.067 (-0.09 to 0.24)	-1.3 (-6.3 to 2.0) <i>P</i> =0.39
Letter Fluency	-3.303 (-5.46 to -1.09)	0.053 (-0.07 to 0.21)	-1.4 (-8.8 to 2.0) <i>P</i> =0.37
Stroop	1.476 (-0.43 to 3.45)	0.008 (-0.05 to 0.08)	0.2 (-7.5 to 15.0) <i>P</i> =0.80
Category Fluency	-0.476 (-1.30 to 0.37)	0.022 (-0.04 to 0.09)	-2.6 (-65.8 to 51.0) <i>P</i> =0.63

Definition of abbreviations: CI = Confidence Interval; DSST = Digit Symbol Substitution Test; MoCA = Montreal Cognitive Assessment; RAVLT = Rey Auditory Verbal Learning Test; Stroop = Stroop Test.

e-Table 8: Comparison of baseline characteristics between those included in the analysis and those excluded due to year 25 non-attendance or missing chest CT at the year 25 examination, year 30 non-attendance or missing cognitive testing at the year 30 examination or missing of key covariates. Data shown as mean (standard deviation) or n (%).

	Included in analysis (n=2,491)	Not included (n=2,623)	P value
Age, years	25.1 (3.6)	24.6 (3.7)	<0.01
Female	1,427 (57.3%)	1,360 (51.9%)	<0.01
Race			<0.01
Black	1,146 (46.0%)	1,491 (56.8%)	
White	1,345 (54.0%)	1,132 (43.2%)	
Height, cm	170.3 (9.5)	170.4 (9.5)	0.48
BMI, kg/m ²	24.4 (4.7)	24.6 (5.3)	0.06
Education, years	14.1 (2.2)	13.5 (2.2)	<0.01
Smoking Status			<0.01
Never	1,538 (62.1%)	1,318 (50.7%)	
Former	336 (13.6%)	340 (13.1%)	
Current	604 (24.4%)	942 (36.2%)	
FEV ₁ , L	3.57 (0.79)	3.53 (0.77)	0.04
FVC, L	4.33 (1.02)	4.27 (1.0)	0.04
FEV ₁ /FVC ratio	0.83 (0.065)	0.83 (0.065)	0.81

Definition of abbreviations: BMI = body mass index; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity.