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ORIGINAL RESEARCH

# Carotid Artery Stiffness is Associated With Cognitive Performance in Former Smokers With and Without Chronic Obstructive Pulmonary Disease

Karin F. Hoth, PhD; Kerrie L. Moreau, PhD; Howard D. Weinberger, MD; Kristen E. Holm, PhD, MPH; Kimberly Meschede, MS; James D. Crapo, MD; Barry J. Make, MD; David J. Moser, PhD; Elizabeth Kozora, PhD; Russell P. Bowler, MD, PhD; Gary L. Pierce, PhD; Patrick Ten Eyck, PhD; Frederick S. Wamboldt, MD

**BACKGROUND:** Heavy smokers perform worse on neuropsychological assessment than age-matched peers. However, traditional pulmonary measures of airflow limitation and hypoxemia explain only a modest amount of variance in cognition. The current objective was to determine whether carotid artery stiffness is associated with cognition in former smokers beyond the effects of amount of smoking and pulmonary function.

**METHODS AND RESULTS:** Eighty-four former smokers including individuals across a spectrum of airflow limitation severity were included: 30 without chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 0 with normal spirometry and lung computed tomography), 31 with mild-moderate chronic obstructive pulmonary disease (GOLD 1–2), and 23 with severe-very severe chronic obstructive pulmonary disease (GOLD 3–4). Participants completed questionnaires, spirometry, carotid ultrasonography, and neuropsychological testing. Multiple linear regression was used to determine whether carotid artery stiffness is associated with neuropsychological performance in 4 cognitive domains after adjusting for age, sex, pack-years of smoking, estimated premorbid intellectual functioning, and airflow limitation. Higher carotid artery β-stiffness index was associated with reduced executive functioning-processing speed in the fully adjusted model (β=−0.49, SE=0.14; $P$=0.001). Lower premorbid intellectual function, male sex, and presence of airflow limitation (GOLD 1 or 2 and GOLD 3 or 4) were also associated with worse executive functioning-processing speed. β-Stiffness index was not significantly associated with performance in other cognitive domains.

**CONCLUSIONS:** Carotid artery stiffness is associated with worse performance on executive functioning-processing speed in former smokers beyond the effects of aging, amount of past smoking, severity of airflow limitation, and hypoxemia. Future research should examine whether carotid stiffness can be used to identify former smokers at risk for subsequent cognitive impairment.

**Key Words:** carotid artery stiffness ■ chronic obstructive pulmonary disease ■ cognition ■ smoking

Chronic heavy tobacco smoking has known deleterious effects on multiple organ systems including the brain.[1] Heavy smokers[2–5] including those with chronic obstructive pulmonary disease (COPD)[6,7] perform worse on cognitive measures than their age-matched peers, particularly on executive

Correspondence to: Karin F. Hoth, PhD, University of Iowa, 200 Hawkins Drive, W278GH, Iowa City, IA 52242. Email: karin-hoth@uiowa.edu

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## CLINICAL PERSPECTIVE

### What Is New?

- The current study is the first to demonstrate that carotid artery stiffness is associated with variability in executive function and processing speed in former smokers with no known history of cognitive impairment.

### What Are the Clinical Implications?

- Further research should examine whether carotid arterial stiffness is a useful clinical marker of risk for cognitive impairment in chronic obstructive pulmonary disease.
- Ultimately, early interventions to enhance the health of central elastic arteries could preserve cognition in smokers with chronic obstructive pulmonary disease.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AIC** | Akaike information criterion |
| **BNT** | Boston Naming Test |
| **BP** | blood pressure |
| **BVMT-R** | Brief Verbal Memory Test-Revised |
| **COPDGene** | Genetic Epidemiology of COPD |
| **COWA** | Controlled Oral Word Association |
| **CVLT-II** | California Verbal Learning Test-II |
| **$FEV_1$** | forced expiratory volume in the first second of expiration |
| **GOLD** | Global Initiative for Chronic Obstructive Lung Disease |
| **HADS** | Hospital Anxiety and Depression Scale |
| **ICS** | inhaled corticosteroid |
| **MCI** | mild cognitive impairment |
| **SABA** | short-acting β-agonist |
| **SCWT** | Stroop Color and Word Test |
| **TMT** | Trail Making Test |
| **VOT** | Hooper Visual Organization Test |
| **WAIS-IV** | Wechsler Adult Intelligence Scale IV |
| **WRAT4** | Wide Range Achievement Test 4 |

functioning, processing speed, and memory retrieval tasks. The presence of cognitive impairment among patients with COPD is associated with worse clinical outcomes[8–10] and difficulty with self-management behaviors including medication adherence.[11,12] Older adults are living longer with smoking-related lung diseases, and thus identifying potentially modifiable mechanisms that drive cognitive impairment in the context of this common risk factor is an important public health priority.

Research into the mechanisms that underlie cognitive impairment in COPD has primarily focused on hypoxemia, which is associated with cognitive impairment in patients with advanced disease.[7,13,14] However, cognitive deficits are present among smokers who have normal blood oxygenation,[15] suggesting that factors other than hypoxemia also affect the brain, particularly among smokers who have not yet manifest clinically evident smoking-related lung disease, a critical period for intervention to prevent cognitive impairment. The earliest physiological changes that occur in COPD (often before clinical manifestation of symptoms) are driven by an enhanced chronic inflammatory response that is associated with small airway disease[16] and vascular abnormalities.[17–21] The need to examine mechanisms beyond hypoxemia that affect the brain in chronic smokers with COPD, including vascular dysfunction, has been highlighted in several review articles.[22–24]

Central artery stiffness is a strong predictor of reduced cognitive performance, altered cerebral white matter integrity, and incident stroke in middle-aged and older adults.[25–30] Stiffening of the carotid arteries is thought to impair their ability to buffer augmented pulsatile hemodynamic pressure for downstream cerebral vessels,[31,32] particularly in subcortical regions of the brain that support executive functioning and processing speed. Greater pressure pulsatility damages the cerebral microcirculation and contributes to white matter hyperintensities and cerebral microbleeds. However, no studies have considered the association between carotid artery stiffness and cognition in patients with COPD and/or included arterial stiffness and pulmonary measures of airflow limitation and hypoxemia together in the same study.

In the current study, we examined whether carotid artery stiffness was associated with neuropsychological performance in former heavy smokers after considering the potential effects of aging, cumulative past smoking history, symptoms of depression and anxiety, antihypertensive and inhaled corticosteroid medication use, blood pressure (BP), and traditional measures of COPD severity (ie, airflow limitation and hypoxemia). We recruited former chronic smokers (>10 pack-year history) with a broad spectrum of underlying lung physiology (ie, smokers ranging from patients without overt smoking-related disease to patients with manifest illness and very severe airflow limitation). This enabled us to examine the effects of physiological measures on neuropsychological

performance while controlling for past smoking history and avoiding potential acute effects of smoking on vascular function. We hypothesized that greater carotid artery stiffness would be associated with reduced performance in the executive functioning-processing speed cognitive domain after adjusting for demographic and clinical covariates. The expectation that there would be effects in executive functioning-processing speed was based on existing literature demonstrating that these cognitive functions are particularly susceptible to changes in carotid artery stiffness.[32–36]

## METHODS

The study was approved by the National Jewish Health institutional review board. Participants provided written documentation of the informed consent process before participating.

### Participant Recruitment

Participants were recruited from the COPDGene study[37] cohort at National Jewish Health in Denver, Colorado. Given that smoking acutely alters vascular function, the current study included only former smokers with nonsmoking status confirmed by urine cotinine assays. Detailed inclusion and exclusion criteria are presented in Table S1. Participants were required to have at least an eighth grade education, speak English, have normal corrected hearing and vision, and have stopped smoking at least 3 months before the study. Exclusion criteria included self-report of a previous diagnosis with a cognitive disorder (eg, dementia, mild cognitive impairment [MCI], neurodevelopmental disorder [ie, autism], or a learning disorder [ie, reading disorder, attention deficit hyperactivity disorder]); neurological disorder (eg, stroke, movement disorder); traumatic brain injury with loss of consciousness >10 minutes; major psychiatric disorder (eg, schizophrenia, bipolar disorder, substance use disorder other than tobacco use); change in treatment for depression or anxiety in the previous 3 months; major medical condition other than COPD or asthma (eg, renal failure, active cancer); arrhythmia; left-sided heart failure; and COPD exacerbation within the past month that required a physician or emergency department visit and/or treatment with antibiotics or oral corticosteroids.

A total of 104 former smokers were enrolled. Three of the 104 patients who attended the first study visit were withdrawn from further participation: 2 for clinically significant hypertension at the time of their initial study visit and 1 for a medication change after visit 1. A total of 101 participants completed 2 study visits. Seventeen participants were excluded from the current analysis: 2 patients who were current users of nicotine identified via urine cotinine, 3 patients classified as having Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0 with evidence of significant emphysema and air trapping on their past COPDGene phase 1 lung computed tomography, 3 patients who met exclusion criteria identified during study visits (1 substance use, 2 traumatic brain injury), 2 outliers with regard to age, 2 patients whose carotid ultrasound scans were not analyzable because of carotid plaques, 4 patients with vision problems that interfered with cognitive testing, and 1 patient who opted to discontinue several cognitive tasks. This analysis included 84 former smokers: 30 without GOLD-defined COPD based on spirometry (GOLD 0) who had normal lung computed tomography (ie, <5% emphysema [percentage of voxels –950 HU on inspiratory scan] and <20% air trapping [percentage of voxels <–856 HU on expiratory scan] on their COPDGene phase 1 lung computed tomography), 31 with mild-moderate COPD (4 GOLD stage 1, 27 GOLD stage 2), and 23 with severe-very severe COPD (13 GOLD stage 3, 10 GOLD stage 4).

### Procedures and Measures

Participants completed 2 study visits that were scheduled within 2 weeks of one another (median=4 days apart, SD=7 days). Data used in the current analysis were collected separately from COPDGene study visits and occurred a median of 2.4 years after their COPDGene phase 1 visit. Figure 1 presents the timing of measures included in the current study: vitals, self-reported medical history and current medication use, symptom questionnaires, prebronchodilator and postbronchodilator spirometry, resting oximetry, urine cotinine, carotid ultrasound, and neuropsychological testing.

#### *Prebronchodilator and Postbronchodilator Spirometry*

Spirometry was performed with an EasyOne spirometer (ndd, Medical Technologies, Inc.), in accordance with American Thoracic Society guidelines.[38] After baseline forced vital capacity testing, 2 puffs of albuterol (180 μg) were administered from a metered dose inhaler with a spacer. After 20 minutes the participants were prompted to perform 3 additional acceptable forced vital capacity maneuvers. Results of questionable quality (≤C rating) were reviewed by a pulmonologist (B.J.M.). For 1 of the 84 participants, previous spirometry results from the individuals' phase 1 COPDGene visit were entered because of suboptimal quality of current spirometry. Postbronchodilator forced expiratory volume in the

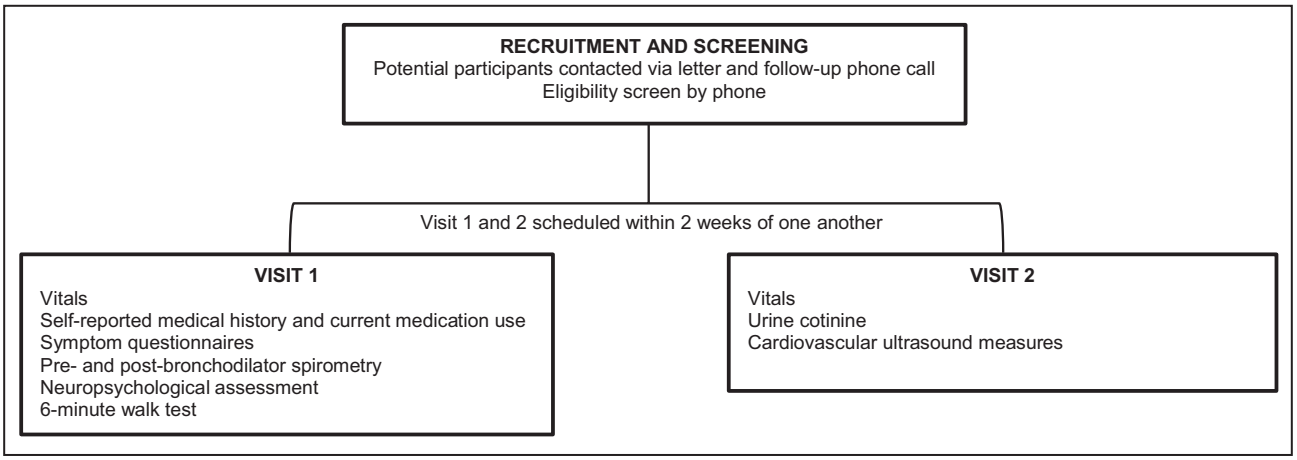


**Figure 1. Study activities by visit.**

first second of expiration ($FEV_1$)/forced vital capacity and $FEV_1$% predicted were used to classify severity of airflow limitation using GOLD criteria.[39]

### Carotid Artery Stiffness

After participants were brought to the cardiovascular assessment room and equipment was arranged, participants were required to lay quietly supine for 10 minutes before vascular data collection began. First, brachial artery pressures were measured using a semiautomated device (Dinamap, Johnson & Johnson). Three measures that were within 5 mm Hg were averaged. Immediately after, carotid artery imaging was performed using high-resolution ultrasound as previously described.[40–43] Briefly, a longitudinal image of the cephalic portion of the carotid artery was acquired ≈1 to 2 cm distal to the carotid bulb. Carotid images were analyzed for systolic and diastolic diameters using computerized semiautomated edge-detection software, which allows accurate identification and measurements of carotid artery lumen diameter over a length of the artery (Vascular Analysis Tools v. 5.5, Medical Imaging Applications). All images were coded by number, blinded to group, and analyzed by the same individual (K.F.H.) with measures confirmed by K.L.M. The coefficient of variation and intraclass correlation coefficient for trial-to-trial reliability measured in 13 individuals for carotid artery diameter, carotid artery distention, pulse pressure, and carotid artery compliance were 0.7% and 0.99, 4.2% and 0.99, 3.7% and 0.97, and 3.1% and 0.99, respectively. β-Stiffness index was used as the primary measure of interest as it provides an index of central arterial stiffness adjusted for distending pressure.[44] Carotid compliance and carotid distensibility coefficient, alternative measures of carotid artery stiffness, were also calculated and were included as secondary measures to be examined in sensitivity analyses by rerunning the model replacing β-stiffness index with compliance and distensibility coefficient.

### Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was used to measure the severity of symptoms of depression and anxiety.[45] The HADS has been used in many studies of COPD.[46–48] The total score ranges from 0 to 21, with scores <14 considered "normal." In this sample, Cronbach α was 0.84.

### Neuropsychological Assessment

Neuropsychological tests were administered and scored by a trained research assistant using standard administration and scoring criteria under the supervision of a clinical neuropsychologist (K.F.H.). The Mini-Mental State Examination 2 (MMSE-2)[49] was administered to characterize the global cognitive status of participants. Consistent with common practice in neuropsychological assessment,[50–52] single word reading (ie, Wide Range Achievement Test 4 [WRAT4] Reading Standard Score[53]) was included as an indicator of premorbid intellectual functioning. Both years of education and WRAT4 Reading Standard Score were included in the Akaike Information Criterion (AIC) process to identify optimal covariates for inclusion in the primary model as described in the Statistical Analysis section below. Other individual neuropsychological test scores were grouped a priori into 4 broad cognitive domains (ie, executive function-processing speed, memory, language, and visuospatial skills) based on past literature[54–57] to reflect the cognitive functions most strongly tapped by each task.

1. *Executive functioning-processing speed*: Trail Making Test (TMT) Part B, Controlled Oral Word Association (COWA), Stroop Color and Word Test

(SCWT)–Interference, Wechsler Adult Intelligence Scale IV (WAIS-IV) coding;
2. *Memory*: California Verbal Learning Test-II (CVLT-II) Trials 1 to 5 immediate recall, Brief Visuospatial Memory Test-Revised (BVMT-R) Trials 1 to 3 total immediate recall, CVLT-II delayed free recall, BVMT-R Trials 1 to 3 delayed free recall;
3. *Language*: Boston Naming Test (BNT), Category Fluency; and
4. *Visual-spatial skills*: WAIS-IV Block Design, Hooper Visual Organization Test (VOT).

A description of each neuropsychological task is available in Table 1. Raw scores were transformed into t-scores (mean of 50 and SD of 10), using previously published age-referenced normative data for healthy adults as cited in Table 1.[58–65] Domain scores were calculated as the mean of the normatively derived t-scores for all of the tests in that domain. Thus, a domain score of 50 indicates exactly average performance, with a score of 40, for example, indicating performance that is 1 SD below the mean relative to healthy age-matched peers.

## Statistical Analysis

Data were analyzed using SAS 9.4 (SAS Institute Inc) and SPSS 25 (SPSS Inc). The data that support the findings of this study are available from the corresponding author upon reasonable request. An α level of 0.05 was set a priori as the criterion for statistical significance for all analyses. Summary statistics for demographic and health characteristics were stratified by severity of airflow limitation (GOLD stage) and assessed for differences using ANOVA for continuous variables and chi-square for categorical variables, which are presented in Tables 2 and 3.

### AIC Process to Identify Relevant Covariates

The following demographic and clinical variables were considered as potential covariates in the primary regression models: age, sex, pack-years, estimated premorbid intelligence quotient (WRAT4 Reading Standard Score), years of education, symptoms of depression and anxiety (HADS Total Score), current antihypertensive use, current inhaled medication use (short-acting β-agonist and/or corticosteroid monotherapy or combination therapy), supine systolic BP, mean arterial pressure, resting seated heart rate, resting seated partial pressure of oxygen ($PO_2$), severity of airflow limitation as grouped by GOLD stage (ie, mild-moderate airflow limitation [GOLD 1 or 2] and severe-very severe airflow limitation [GOLD 3 or 4] with GOLD 0 normal lung as the reference), and airflow limitation con-

**Table 1. Description of Neuropsychological Tasks by Cognitive Domain With References to Age-Adjusted Normative Data Used for Scoring**

| | Assesses |
|---|---|
| Executive Functioning-Processing Speed Domain | |
| Trail Making Test Part B[58] | This test measures cognitive flexibility and sequencing. It involves connecting randomly arranged numbers and letters on a page |
| Controlled Oral Word Association[59] | This test measures ability to initiate and maintain effort. It involves rapidly producing words beginning with specified letters |
| Stroop Color and Word Test–Interference[60] | This test measures ability to shift perceptual sets and inhibit overlearned responses. It involves stating the ink color in which an incongruent word is printed. For example, the word "red" is printed in green ink |
| Wechsler Adult Intelligence Scale IV Coding[61] | This test measures psychomotor speed and visual-motor coordination. It involves matching symbols with numbers according to a key at the top of the page and thus includes an executive functioning component[54] |
| Memory domain | |
| California Verbal Learning Test-II[62] Trials 1–5 Immediate Recall | Immediate recall of a list of words |
| Brief Visuospatial Memory Test-Revised[63] Trials 1–3 Total Immediate Recall | Immediate recall of a display of figures |
| California Verbal Learning Test-II[62] Delayed Free Recall | Delayed recall for a list of words |
| Brief Visuospatial Memory Test-Revised[63] Delayed Free Recall | Delayed recall of a display of figures |
| Language Domain | |
| Boston Naming Test[64] | Ability to name pictures of objects |
| Category Fluency[65] | Timed word generation task based on a category (ie, animals) |
| Visuospatial Skill Domain | |
| Wechsler Adult Intelligence Scale IV Block Design[61] | Visuospatial construction and visual abstract problem solving using blocks |
| Hooper Visual Organization Test[66] | Ability to visually integrate information into whole perceptions |

**Table 2. Demographic and Clinical Characteristics of Participants Grouped by GOLD Stage**

| | All Participants (N=84) | Former Smokers | | | *P* Value |
|---|---|---|---|---|---|
| | | No COPD (n=30) | GOLD 1 or 2 (n=31) | GOLD 3 or 4 (n=23) | |
| Demographic and pulmonary variables | | | | | |
| Age, y | 69.2 (6.9) | 67.0 (6.5) | 70.7 (7.2) | 69.9 (6.6) | 0.90 |
| Women, No. (%) | 36 (43) | 12 (40) | 13 (42) | 11 (48) | 0.84 |
| Education, y | 14.2 (2.3) | 14.7 (2.4) | 13.9 (2.2) | 14.1 (2.3) | 0.35 |
| Estimated Premorbid Intelligence (WRAT4 Reading Standard Score) | 101.2 (7.4) | 99.8 (8.3) | 102.4 (7.7) | 101.5 (5.7) | 0.39 |
| MMSE-2 raw score | 28.1 (1.6) | 28.6 (1.5) | 27.8 (1.4) | 27.8 (1.7) | 0.08 |
| Smoking history, pack-y* | 51.6 (33.6)* | 37.8 (23.9)* | 58.1 (42.2)* | 60.7 (25.7)* | 0.02* |
| Depression and anxiety (HADS) | 7.0 (5.0) | 5.5 (3.5) | 7.1 (5.4) | 8.7 (5.6) | 0.06 |
| Postbronchodilator spirometry | | | | | |
| $FEV_1$/forced vital capacity, % | 62.0 (16.0) | 78.7 (4.9) | 60.3 (6.6) | 42.4 (9.9) | ··· |
| $FEV_1$% predicted | 67.0 (27.0) | 92.3 (18.7) | 66.5 (13.4) | 34.9 (9.7) | ··· |
| Seated $PO_2$ (under usual treatment) | 93.3 (3.1) | 94.2 (2.8) | 92.5 (2.4) | 93.3 (3.9) | 0.10 |
| Oxygen use at visit, No. (%)*** | 27 (33)*** | 0 (0)*** | 7 (25)*** | 20 (87)*** | <0.001*** |
| Vascular measures | | | | | |
| Supine systolic BP, mm Hg | 125.5 (11.7) | 122.9 (12.4) | 129.0 (10.2) | 124.2 (11.8) | 0.10 |
| Supine diastolic BP, mm Hg | 74.3 (8.6) | 72.9 (8.6) | 74.9 (8.7) | 75.3 (8.6) | 0.54 |
| Supine mean arterial pressure, mm Hg | 91.4 (8.6) | 89.6 (9.3) | 93.0 (8.0) | 91.6 (8.7) | 0.31 |
| Supine heart rate, beats per min* | 63.0 (10.4)* | 58.9 (9.8)* | 63.9 (9.6)* | 67.2 (10.7)* | 0.01* |
| Carotid distension, mm | 0.4 (0.1) | 0.5 (0.1) | 0.4 (0.1) | 0.4 (0.1) | 0.06 |
| Carotid end-diastolic diameter, mm | 7.0 (0.9) | 6.9 (0.9) | 7.0 (0.8) | 7.1 (1.0) | 0.76 |
| Carotid β-stiffness Index, U* | 9.4 (3.9)* | 8.1 (2.5)* | 10.9 (4.7)* | 9.1 (3.6)* | 0.02* |
| Carotid compliance, $mm^2$/mm Hg×$10^{-1}$ | 0.97 (0. 40) | 1.07 (0.42) | 0.83 (0.32) | 1.03 (0.45) | 0.05 |
| Carotid distensibility coefficient, kPa×$10^{-3}$* | 19.0 (7.2)* | 21. 6 (7.9)* | 16.1 (6.0)* | 19.3 (6.5)* | 0.01* |
| Medication use | | | | | |
| Antihypertensives, No. (%) | 43 (51) | 13 (43) | 19 (61) | 11 (48) | 0.35 |
| ACEIs, No. (%) | 15 (18) | 5 (17) | 5 (16) | 5 (22) | 0.85 |
| CCBs, No. (%) | 9 (11) | 2 (7) | 4 (13) | 3 (13) | 0.67 |
| β-Blockers, No. (%) | 18 (21) | 7 (23) | 8 (26) | 3 (13) | 0.50 |
| Diuretics, No. (%) | 19 (23) | 7 (23) | 8 (26) | 4 (17) | 0.76 |
| Inhaled medication (SABA and/or ICS therapy), No. (%)*** | 41 (49)*** | 3 (10)*** | 19 (61)*** | 19 (83)*** | <0.001*** |
| Inhaled SABA, No. (%)* | 20 (24)* | 2 (7)* | 9 (29)* | 9 (39)* | 0.02* |
| ICS monotherapy, No. (%) | 12 (14) | 2 (7) | 6 (19) | 4 (17) | 0.32 |
| ICS/long-acting β-agonist combination, No. (%)*** | 26 (31)*** | 0 (0)*** | 11 (36)*** | 15 (65)*** | <0.001*** |

*P* values reflect omnibus comparisons (ANOVA or chi-square) across the 3 airflow limitation groups. *P* values are not reported for forced expiratory volume in the first second of expiration ($FEV_1$)/forced vital capacity or $FEV_1$% predicted as they are used to define Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups. ACEIs indicates angiotensin-converting enzyme inhibitors; BP, blood pressure; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale; ICS, inhaled corticosteroid; $PO_2$, partial pressure of oxygen; SABA, short-acting β-agonist; MMSE-2, Mini-Mental State Examination 2; and WRAT4, Wide Range Achievement Test 4.

*$P$<0.05, **$P$<0.01, ***$P$<.0.001.

sidered continuously (ie, postbronchodilator $FEV_1$% predicated).[53,54]

All possible predictor combinations of maximum order 7 were fit to each of the 4 cognitive domain-dependent variables (executive function-processing speed, memory, language, and visuospatial skills) and compared using AIC. A smaller AIC value indicates better model fit. The model with the fewest covariates that was within 2 of the smallest AIC was selected. This process statistically weighs a 2-unit penalty term with the improvement in model fit for each variable added, balancing goodness-of-fit with parsimony, while maintaining generalizability. We chose this approach to ensure that our primary regression models

**Table 3. Neuropsychological Performance of Former Smokers With and Without COPD by Cognitive Domain t-Score**

| Cognitive Domain | All Participants (N=84) | | | Former Smokers | | | | | | | | | *P* Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No COPD (n=30) | | | GOLD 1 or 2 (n=31) | | | GOLD 3 or 4 (n=23) | | | |
| | Mean (SD) | Minimum | Maximum | Mean (SD) | Minimum | Maximum | Mean (SD) | Minimum | Maximum | Mean (SD) | Minimum | Maximum | |
| Executive Function-Processing Speed* | 48.4 (5.7)* | 36.3 | 66.8 | 50.7 (5.5)* | 41.9 | 65.2 | 47.7 (6.0)* | 36.3 | 66.8 | 46.5 (4.7)* | 37.6 | 55.1 | 0.02* |
| Memory | 48.6 (8.4) | 26.0 | 63.8 | 50.2 (9.1) | 26.0 | 63.8 | 49.1 (7.9) | 28.3 | 61.8 | 45.8 (7.9) | 27.8 | 59.0 | 0.16 |
| Language | 52.1 (7.0) | 38.3 | 70.0 | 54.2 (7.5) | 38.3 | 65.0 | 50.9 (5.9) | 38.3 | 63.3 | 51.1 (7.2) | 40.0 | 70.0 | 0.14 |
| Visuospatial skills | 52.3 (6.0) | 39.8 | 66.3 | 52.3 (6.8) | 39.8 | 64.2 | 52.2 (6.3) | 41.7 | 66.3 | 52.5 (4.7) | 44.3 | 64.8 | 0.99 |

COPD indicates chronic obstructive pulmonary disease; and GOLD, Global Initiative for Chronic Obstructive Lung Disease.

The t-scores were calculated using previously published normative data adjusted for age and have a mean of 50 and an SD of 10. See Table 1 for further information on tasks included in each domain score and references for norms that were utilized in scoring.

*$P<0.05$.

were not over fit, reducing power, given our modest sample size of 84.

### *Primary Analysis: Multiple Linear Regression Examining the Association Between Carotid Artery Stiffness and Neuropsychological Performance*

Four regression models were generated: 1 for each of the 4 neuropsychological domains (ie, executive-function processing speed, memory, language, and visuospatial skills). Neuropsychological domain t-score was the dependent variable in each model. Independent variables included in each model were the variables identified via the AIC best model approach for that cognitive domain. Independent variables were entered simultaneously; thus, regression coefficients and significance tests for each independent variable reflect the effect of that variable after accounting for the effect of all other independent variables in the model.

## RESULTS

### Characteristics of Participants

Descriptive information is presented in Table 2. Participants were aged ≈70 years, had 14 years of formal education on average, with estimated average premorbid intellectual functioning (mean WRAT4 Reading Standard Score=101), and intact MMSE-2 scores (above the commonly accepted cutoff of 23, mean MMSE-2 score=28). Around 40% of participants were women, with minimal current symptoms of depression and anxiety (HADS). All participants reported quitting smoking at least 6 months before their current study visits (median=15 months before the study; range 6 months to 64 years prior). There were no statistically significant differences between the airflow limitation groups for age, sex distribution, education, or estimated premorbid intelligence quotient (Table 2). The groups did not differ on resting $PO_2$; however, nearly 90% of participants with severe-very severe COPD were using daytime oxygen, and $PO_2$ was collected under typical oxygen treatment conditions for each participant. Participants with COPD had a higher pack-year smoking history than participants without COPD. There were statistically significant differences across airflow limitation group for heart rate [$F(2,81)=4.7$, $P=0.01$], β-stiffness index [$F(2,81)=4.3$, $P=0.02$], carotid distensibility coefficient [$F(2,81)=4.8$, $P=0.01$], and performance on the executive functioning-processing speed cognitive domain [$F(2, 81)=4.3$, $P=0.02$; Table 3]. The groups differed regarding rates of use of inhaled medications including corticosteroids and β-agonist medications; however, there were no statistically significant differences for antihypertensive medication use between the groups (Table 2).

## Association Between Carotid Artery Stiffness and Cognition

The optimal multiple linear regression model for executive function-processing speed as determined by AIC included the following covariates: carotid artery stiffness (β-stiffness index), severity of airflow limitation as grouped by GOLD stage, pack-years, estimated premorbid intelligence quotient (WRAT4 Reading Standard Score), and sex as presented in Table 4. Higher β-stiffness index was associated with lower performance on the executive function-processing speed domain (β=−0.49, *P*=0.001). On average, for every 1-unit increase in β-stiffness index, there was a 0.49-point decrease in executive function-processing speed t-score after adjusting for all of the other predictors in the model. The following covariates were associated with lower executive function-processing performance: lower premorbid intelligence quotient, male sex, higher pack years of smoking history, and severity of airflow limitation measured by GOLD stage of COPD (GOLD 1 or 2 and GOLD 3 or 4). To illustrate the association between β-stiffness index and executive function-processing speed t-score, Figure 2 presents the unadjusted scatterplot between the variables.

β-Stiffness index was not significantly associated with performance in the other cognitive domains (ie, memory, language, and visuospatial skills). The adjusted regression models for memory, language, and visuospatial skill domains are presented in Tables S2 through S4. These models included covariates identified as significant in the AIC analysis for each domain individually and, as noted above, did not include β-stiffness index as it was not significant in AIC analyses for these domains.

In post hoc analyses we reran the primary regression model replacing β-stiffness index with carotid compliance and carotid distensibility coefficient to determine whether these alternative parameters of stiffness might be more strongly associated with executive function processing speed. In these post hoc models we additionally included mean arterial pressure and heart rate because carotid compliance and carotid distensibility coefficient are thought to be more dependent on BP than β-stiffness index. Carotid artery compliance was not significantly associated with executive function-processing speed in the full model (β=0.12, *P*=0.28). Carotid distensibility coefficient was statistically significantly associated with executive function-processing speed in the full model (β=0.23, *P*=0.03), but the AIC statistic was higher than that for β-stiffness index, indicating that β-stiffness was a better predictor of executive function-processing speed than distensibility coefficient. These models that included carotid artery compliance and carotid distensibility coefficient as independent variables in place of β-stiffness index are presented as Tables S5 and S6.

Finally, in post hoc analyses we reran the primary regression model examining the effect of β-stiffness index on the 4 individual tests that comprised the executive function-processing speed domain (ie, SCWT, TMT

**Table 4. Results of Simultaneous Multiple Linear Regression Model to Predict Executive Functioning-Processing Speed in Former Smokers (N=84)**

| Independent Variable | Unstandardized β | Standardized β | 95% CI | | SE | *P* Value |
|---|---|---|---|---|---|---|
| | | | Lower Bound | Upper Bound | | |
| Sex | | | | | | |
| Men | Reference | Reference | | | | |
| Women*** | 3.77*** | 0.33*** | 1.72*** | 5.82*** | 1.03*** | <0.001*** |
| Smoking history (pack-y) | 0.03 | 0.15 | −0.01 | 0.06 | 0.02 | 0.12 |
| Estimated Premorbid Intelligence (WRAT4)*** | 0.26*** | 0.33*** | 0.12*** | 0.39*** | 0.07*** | <0.001*** |
| Severity of airflow limitation by GOLD stage | | | | | | |
| No COPD (GOLD 0–normal lung computed tomography) | Reference | Reference | | | | |
| Mild-moderate (GOLD 1 or 2)* | −2.93* | −0.25* | −5.48* | −0.37* | 1.28* | 0.03* |
| Severe-very severe (GOLD 3 or 4)*** | −5.05*** | −0.40*** | −7.73*** | −2.38*** | 1.35*** | <0.001*** |
| Carotid β-stiffness index, U** | −0.49** | −0.33** | −0.76** | −0.21** | 0.14** | 0.001** |

Overall model: F=8.1 (*P*<0.001). Dependent variable=Executive Functioning-Processing Speed domain t-score calculated using age-adjusted normative data (see Table S2 for norm references). Covariates were selected based on Akaike information criterion analysis for Executive Functioning-Processing Speed t-score as described in the Methods and Results sections. COPD indicates chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; and WRAT4, Wide Range Achievement Test 4.

*$P<0.05$, **$P<0.01$, ***$P<0.001$.

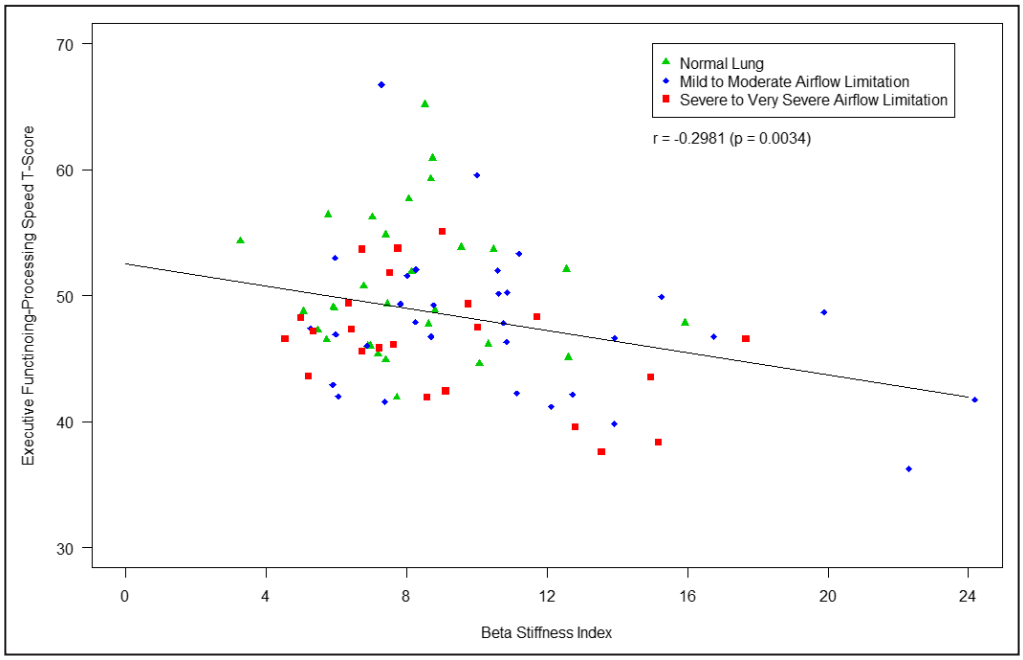


**Figure 2. Scatterplot of the association between central artery stiffness and executive function-processing speed in former smokers.**

Part B, COWA, and WAIS-IV Coding). These models were calculated to determine whether there was consistency of the effect of β-stiffness index across tasks in our domain of interest. In the fully adjusted models, β-stiffness index was significantly associated with performance on 3 of the 4 tasks (ie, [1] SCWT: β-stiffness index β=−0.23, *P*=0.01; [2] TMT Part B: β-stiffness index β=−0.33, *P*=0.003; and [3] COWA: β-stiffness index β=−0.24, *P*=0.03). The effect of β-stiffness index for WAIS-IV coding was not statistically significant. The results for these 4 regression models are available in Tables S7 through S10.

## DISCUSSION

This study is the first to examine the impact of carotid artery stiffness on cognition among former smokers with and without COPD and the first to include pulmonary and vascular measures together in the same model. Participants were former heavy smokers (>10 pack-year history) recruited with the goal of spanning the full spectrum of lung function (ie, normal lung function without COPD to very severe airflow limitation) who had no known history of a neurological or cognitive disorder. This approach allowed us to examine physiology across former smokers, while also adjusting for cumulative amount of smoking history in our model. Consistent with previous studies, airflow limitation (specifically the presence of airflow limitation as defined by GOLD criteria stage 1 or 2 and 3 or 4) was associated with worse performance on measures of executive function-processing speed. The new finding in the current study is that higher carotid artery stiffness expressed as carotid β-stiffness index was associated with reduced performance on neuropsychological measures of executive function-processing speed after adjusting for demographic and clinical characteristics including age, sex, an estimate of premorbid intellectual functioning, amount of smoking history, hypoxemia, and severity of airflow limitation. We considered the potential effect of BP in our analysis but found that BP was not independently associated with executive function-processing speed in our sample. Carotid β-stiffness index was more strongly associated with executive function-processing speed than carotid distensibility coefficient. In contrast, carotid artery compliance was not associated with executive function-processing speed. The reasons for this are unclear but could be related to different calculations of these expressions of local carotid arterial stiffness. Compliance is a measure of the vessel's buffering capacity and is expressed as the change in carotid lumen diameter for a given change in pressure (pulse pressure) during a cardiac cycle, whereas distensibility coefficient is the compliance normalized to the carotid diastolic diameter.[67]

Large elastic arterial stiffness (here measured in the carotid artery) has been associated with cognitive function in multiple community based samples.[31,68–70] An association between measures of arterial stiffness and evidence of cerebrovascular change on neuroimaging

has also been documented in previous studies.[71–73] Large elastic arteries, such as the aorta and carotid arteries, buffer pulsatile pressure generated from left ventricular ejection and facilitate continuous blood flow during diastole to distal small vessels, particularly high blood flow organs including the brain.[31] Decreased elasticity in the carotid artery may transmit pulsatile pressure deeper into the cerebrovasculature, making these vessels vulnerable to damage from wider pressure fluctuations and susceptible to diastolic bouts of hypoperfusion.[31,69] Frontal-subcortical networks in the brain, which support executive functioning and processing speed, are particularly susceptible to ischemic damage from blood flow or vascular abnormalities.[74–76] The pattern of association between carotid artery stiffness and the domain of executive functioning and processing speed is consistent with previous studies demonstrating that these cognitive functions are particularly susceptible to vascular changes.

The study was designed to focus on smokers who had not come to clinical attention as having cognitive impairment; thus, patients who reported having been diagnosed with dementia or a neurological illness where one might expect global and/or severe cognitive impairment were excluded. As expected given these criteria, the mean cognitive performance of the sample was in the average range and no participants' MMSE-2 score fell below the clinical cut for suspected dementia. Since we did not conduct a multidisciplinary dementia diagnostic review during screening, it is possible that some participants with unrecognized MCI could have been enrolled in the study. To explore this possibility, in post hoc analyses we identified that 4 of the 84 participants' performance in the memory domain was impaired (defined as ≥1.5 SDs below the mean), an approach that provides one way to operationalize domain specific impairment in the absence of comprehensive diagnostic information. No participants' domain score for language, visuospatial function, or executive function-processing speed were impaired using this definition. We repeated the primary analysis excluding these individuals and the findings were unchanged providing some support for the idea that our results were not significantly affected by potentially undiagnosed MCI. The fact that both the presence of airflow limitation and greater carotid artery stiffness were associated with weaker executive functioning-processing speed in this largely cognitively intact sample of former smokers demonstrates that it is possible to detect relations between pulmonary, arterial stiffness, and cognition in the "preclinical" period before severe cognitive impairment develops. Identifying physiological variables, such as arterial stiffness, that are associated with variability in cognitive performance early in the development of COPD is important as those mechanisms can be the focus of subsequent research to determine their long-term impact in longitudinal studies. Ultimately, identifying such mechanisms can lead to targeted interventions for prevention such as early monitoring and treatment of cardiovascular risk factors and atherosclerotic vascular disease for some patients.

## STUDY LIMITATIONS

The findings need to be considered in the context of the limitations of the study. First, our sample size of 84 is modest, which limited our ability to consider potential interactions between severity of COPD and arterial stiffness. The small sample size may have resulted in a failure to detect significant differences for cognitive domain scores beyond executive function-processing speed (where *P* values were at or around 0.14). In future larger samples it will be interesting to examine the possibility that COPD progression contributes to reduced cognition in smokers by magnifying the link between carotid artery stiffness and changes in brain structure and function. Second, neuroimaging was not collected, and, thus, cerebrovascular function (ie, cerebral blood flow and cerebrovascular reactivity) was not directly measured. It will be important for future research to include direct measures of the cerebrovasculature as well as cognitive measures when examining the contribution of arterial stiffness to cognitive performance in smokers and those with smoking-related lung disease. Third, our exclusion criteria were designed to minimize the impact of potentially confounding neurological illnesses and events, which also meant that patients with severe to very severe COPD who had experienced significant cardiovascular complications such as stroke were not eligible. Eliminating those individuals likely reduced the extreme end of the spectrum of patients with the greatest carotid artery stiffness, resulting in less arterial stiffness among our participants with advanced COPD than would be found in an unselected group of patients. The fact that a significant association between carotid artery stiffness and executive functioning-processing speed was observed in the context of the strict inclusion/exclusion criteria while adjusting for multiple covariates increases confidence in the strength of the association. Fourth, we did not conduct a multidisciplinary dementia diagnostic evaluation as a part of our screening procedure, which would have been the ideal way to identify the presence of dementia and MCI. Our initial screening relied on self-report of previous cognitive diagnoses, which is limited by participants' recall, potential hesitance to acknowledge cognitive problems, and by the fact that many individuals with dementia and MCI are not identified in clinical practice. Thus, it is possible that some individuals with unrecognized MCI were

enrolled. The fact that the findings were unchanged after rerunning the primary analysis after removing the 4 individuals with impaired cognitive domain scores suggests that the results were not significantly impacted by potential MCI; however, only a dementia review would conclusively determine whether individuals in the sample meet criteria for MCI. Fifth, calculating carotid stiffness with brachial BPs instead of local carotid BPs may have introduced a bias by underestimating carotid systolic and pulse pressures. Past work conducted by coauthor Moreau et al[77] included data analyzed from a subsample of participants who had carotid artery BP measured via applanation tonometry along with concurrent brachial artery BPs and the approaches resulted in similar values for carotid artery compliance. Additionally, it has been suggested that use of brachial artery BPs and carotid artery pressures by tonometry are fixed, thus leading to a fixed, systematic error in stiffness index.[78] It is possible that the use of brachial BP increased noise in the stiffness estimates, although this would have served to reduce the likelihood of observing an association, which was indeed observed. Finally, the current study did not include a never-smoker control group and, thus, we were not able to examine smoking status in this analysis. It will be essential for future studies to include never-smoker controls and light smokers.

## STUDY STRENGTHS

Despite these limitations, the current study has several strengths and clinical implications. First, including both pulmonary and arterial stiffness measures in the same sample of former smokers is a major advance beyond past literature where these factors have typically been considered separately in relation to cognition. Both severity of airflow limitation measured using spirometry (the classic approach to clinically diagnosing COPD) and carotid artery stiffness accounted for independent variance in executive function-process speed performance. Future research on how smoking impacts the brain should consider both pulmonary and vascular effects of smoking. Second, the fact that carotid artery stiffness was associated with variability in cognitive performance while adjusting for basic demographics, amount of smoking history, resting $PO_2$, and airflow limitation suggests that cognitive performance in COPD is caused by more than reduced pulmonary function alone and is not fully explained by $PO_2$. COPD researchers have previously identified the potential significance of comorbid cardiovascular disease for the brain in COPD and these data are a first step in empirically demonstrating the connection. In our sample of participants selected to have no history of known cognitive impairment, most participants' cognitive t-scores fell within normal limits and thus would not manifest significant function difficulty as a result of cognition. However, if followed over time, we may expect greater cognitive difficulties to manifest for those at risk and, at the population level, interventions to mitigate that risk would be critical to implement. Third, the observation of an association between carotid artery stiffness and cognition in the domain of executive functioning and processing speed is consistent with the idea that brain regions that support executive functioning and processing speed, including subcortical structures and white matter, are particularly vulnerable to higher carotid artery stiffness. Finally, central artery stiffening has been the target of pharmacologic and exercise interventions in COPD.[79–81] Thus, future studies should examine whether implementing treatments that target arterial stiffening could have beneficial effects on cognition in this population. If future longitudinal studies show that patients with COPD and arterial stiffening are at an increased risk for subsequently developing cognitive impairment, this would provide yet more incentive to intervene with treatments to enhance arterial health in COPD.

## ARTICLE INFORMATION

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### Affiliations

From the Psychiatry (K.F.H., D.J.M.), Iowa Neuroscience Institute (K.F.H.), Health and Human Physiology (G.L.P.), Abboud Cardiovascular Research Center (G.L.P.), Environmental Health Sciences Research Center (G.L.P.), and Institute for Clinical and Translational Science (P.T.E.), University of Iowa, Iowa City, IA; Medicine, National Jewish Health, Denver, CO (K.F.H., H.D.W., K.E.H., K.M., J.D.C., B.J.M., E.K., R.P.B., F.S.W.); Medicine (K.L.M., H.D.W., J.D.C., B.J.M., R.P.B.) and Psychiatry (E.K., F.S.W.), University of Colorado Anschutz Medical Campus, Aurora, CO; Community and Behavioral Health, University of Colorado School of Public Health, Aurora, CO (K.E.H.).

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### Disclosures

None.

### Supplementary Materials

**Tables S1–S10**

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# SUPPLEMENTAL MATERIAL

Table S1. Study Inclusion and Exclusion Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • Former smoker with at least a 10 pack-year smoking history<br>• Quit smoking ≥3 months prior to study visits<br>• Age 30-85<br>• ≥8$^{th}$ grade education<br>• Normal/corrected hearing and vision<br>• English Speaker | • Pregnancy or suspected pregnancy<br>• Concomitant respiratory disorder other than asthma<br>• Use of antibiotics/steroids for a COPD exacerbation in past month<br>• Active cancer under treatment<br>• Radiation therapy to the chest<br>• Lung surgery (LVRS, transplant, lobectomy)<br>• Lung cancer known or suspected<br>• Inability to use albuterol<br>• Eye surgery in last 6 weeks<br>• Chest or abdominal surgery in the past 3 months<br>• Heart attack in the last 3 months<br>• Hospitalization for any heart problem in the past month<br>• Chronic kidney failure<br>• Heart failure<br>• Pulmonary hypertension<br>• Neurological disorder including stroke, epilepsy, traumatic brain injury with loss of consciousness>15 minutes, and neurodegenerative movement disorder<br>• Previous diagnosis of dementia or mild cognitive impairment<br>• Previous diagnosis of a neurodevelopmental disorder (i.e., autism) or a learning disorder (i.e., reading disorder, ADHD)<br>• Psychotic disorder<br>• Bipolar disorder<br>• History of treatment for a substance use disorder other than tobacco<br>• Change in psychiatric medication in last 30 days |

Table S2. Results of Simultaneous Multiple Linear Regression Model for the Memory in Former Smokers (N=84)

Overall Model: F=4.12 (p=0.004)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Age** | **-0.28** | **-0.23** | **-0.55** | **-0.006** | **0.14** | **0.045** |
| **Estimated Premorbid IQ (WRAT4)** | **0.41** | **0.36** | **0.17** | **0.66** | **0.12** | **0.001** |
| Severity of Airflow Limitation by GOLD stage | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| Mild-Moderate (GOLD 1-2) | -1.19 | -0.07 | -5.33 | 2.95 | 2.08 | 0.57 |
| Severe-Very Severe (GOLD 3-4) | -4.30 | -0.23 | -8.71 | 0.11 | 2.22 | 0.06 |

Notes: WRAT4= Wide Range Achievement Test 4;
Dependent variable= Memory domain t-score calculated using age-adjusted normative data (see supplemental Table 2 for norm references);
Covariates were selected based on AIC analysis for Memory t-score as described in the methods and results.

Table S3. Results of Simultaneous Multiple Linear Regression Model for the Visuospatial Skills in Former Smokers (N=84)

Overall Model: F=5.8 (p<0.001)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Age** | **0.19** | **0.22** | **0.007** | **0.38** | **0.09** | **0.04** |
| **Estimated Premorbid IQ (WRAT4)** | **0.30** | **0.37** | **0.13** | **0.47** | **0.09** | **<0.001** |
| Severity of Airflow Limitation by GOLD stage | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| Mild-Moderate (GOLD 1-2) | -1.53 | -0.12 | -4.38 | 1.33 | 1.43 | 0.29 |
| Severe-Very Severe (GOLD 3-4) | -0.84 | -0.06 | -3.88 | 2.20 | 1.53 | 0.59 |

Notes: WRAT4= Wide Range Achievement Test 4;
Dependent variable= Visuospatial skills domain t-score calculated using age-adjusted normative data (see supplemental Table 2 for norm references);
Covariates were selected based on AIC analysis for Visuospatial skills t-score as described in the methods and results.

Table S4. Results of Simultaneous Multiple Linear Regression Model for the Language in Former Smokers (N=84)

Overall Model: F=4.41 (p=0.001)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Age** | **-0.28** | **-0.28** | **-0.50** | **-0.06** | **0.11** | **0.01** |
| Smoking History (pack-years) | 0.04 | 0.19 | -0.004 | 0.08 | 0.02 | 0.07 |
| **Estimated Premorbid IQ (WRAT4)** | **0.34** | **0.36** | **0.14** | **0.53** | **0.10** | **0.001** |
| **Depression and Anxiety (HADS Total)** | **-0.38** | **0.27** | **-0.67** | **-0.09** | **0.15** | **0.01** |
| Severity of Airflow Limitation by GOLD stage | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| Mild-Moderate (GOLD 1-2) | -3.27 | -0.23 | -6.69 | 0.15 | 1.72 | 0.06 |
| Severe-Very Severe (GOLD 3-4) | -2.50 | -0.16 | -6.24 | 1.24 | 1.88 | 0.19 |

Notes: WRAT4= Wide Range Achievement Test 4; HADS= Hospital Anxiety and Depression Scale;
Dependent variable= Language domain t-score calculated using age-adjusted normative data (see supplemental Table 2 for norm references);
Covariates were selected based on AIC analysis for Language t-score as described in the methods and results.

Table S5. Results of Simultaneous Multiple Linear Regression Model to Predict Executive Functioning-Processing Speed in Former Smokers Using Carotid Distensibility Coefficient (N=84)

Overall Model: F=5.2 (p<0.001)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Sex** | | | | | | |
| Male | Reference | Reference | | | | |
| **Female** | **4.40** | **0.38** | **2.22** | **6.58** | **1.10** | **<0.001** |
| Smoking History (pack-years) | 0.02 | 0.12 | -0.01 | 0.05 | 0.02 | 0.23 |
| **Estimated Premorbid IQ (WRAT4)** | **0.24** | **0.32** | **0.10** | **0.39** | **0.07** | **0.001** |
| **Severity of Airflow Limitation by GOLD stage** | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| **Mild-Moderate (GOLD 1-2)** | **-3.66** | **-0.31** | **-6.38** | **-0.94** | **1.37** | **0.009** |
| **Severe-Very Severe (GOLD 3-4)** | **-5.41** | **-0.43** | **-8.33** | **-2.49** | **1.47** | **<0.001** |
| Mean Arterial Pressure (MAP; mmHg) | 0.12 | 0.19 | -0.003 | 0.25 | 0.06 | 0.06 |
| Heart Rate (bpm) | 0.02 | 0.03 | -0.10 | 0.13 | 0.06 | 0.78 |
| **Carotid Distensibility Coefficient (kPa x $10^{-3}$)** | **182.84** | **0.23** | **19.82** | **345.87** | **81.84** | **0.03** |

Note: WRAT4= Wide Range Achievement Test 4;
Dependent variable= Executive functioning-processing speed t-score calculated using age-adjusted normative data (see supplemental Table 2 for norm references)

Table S6. Results of Simultaneous Multiple Linear Regression Model to Predict Executive Functioning-Processing Speed in Former Smokers Using Carotid Compliance (N=84)

Overall Model: F=4.5 (p<0.001)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Sex** | | | | | | |
| Male | Reference | Reference | | | | |
| **Female** | **4.55** | **0.40** | **2.23** | **6.87** | **1.16** | **<0.001** |
| Smoking History (pack-years) | 0.02 | 0.10 | -0.02 | 0.05 | 0.02 | 0.34 |
| **Estimated Premorbid IQ (WRAT4)** | **0.25** | **0.33** | **0.10** | **0.40** | **0.08** | **0.001** |
| Severity of Airflow Limitation by GOLD stage | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| **Mild-Moderate (GOLD 1-2)** | **-4.04** | **-0.34** | **-6.81** | **-1.28** | **1.39** | **0.005** |
| **Severe-Very Severe (GOLD 3-4)** | **-5.50** | **-0.43** | **-8.50** | **-2.51** | **1.51** | **<0.001** |
| Mean Arterial Pressure (mmHg) | 0.11 | 0.16 | -0.02 | 0.23 | 0.07 | 0.11 |
| Heart Rate (bpm) | -0.001 | -0.002 | -0.11 | 0.11 | 0.06 | 0.98 |
| Carotid Compliance ($mm^2$/mmHg x $10^{-1}$) | 16.48 | 0.12 | -13.37 | 46.34 | 14.99 | 0.28 |

Note: WRAT4= Wide Range Achievement Test 4;
Dependent variable= Executive functioning-processing speed t-score calculated using age-adjusted normative data (see supplementary Table 2 for norm references)

Table S7. Results of Simultaneous Multiple Linear Regression Model for Stroop Interference in Former Smokers (N=84)

Overall Model: F=2.4 (p=0.04)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Sex** | | | | | | |
| Male | Reference | Reference | | | | |
| Female | 0.17 | 0.01 | -3.17 | 3.52 | 1.68 | 0.92 |
| Smoking History (pack-years) | 0.05 | 0.22 | -0.002 | 0.10 | 0.03 | 0.06 |
| Estimated Premorbid IQ (WRAT4) | 0.15 | 0.14 | -0.07 | 0.38 | 0.11 | 0.18 |
| Severity of Airflow Limitation by GOLD stage | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| Mild-Moderate (GOLD 1-2) | -2.71 | -0.17 | -6.89 | 1.46 | 2.10 | 0.20 |
| Severe-Very Severe (GOLD 3-4) | -4.08 | -0.23 | -8.46 | 0.30 | 2.20 | 0.07 |
| **Carotid β-Stiffness Index (U)** | **-0.60** | **-0.30** | **-1.06** | **-0.15** | **0.23** | **0.01** |

Note: WRAT4= Wide Range Achievement Test 4;
Dependent variable= Executive functioning-processing speed t-score calculated using age-adjusted normative data (see supplementary Table 2 for norm references)

Table S8. Results of Simultaneous Multiple Linear Regression Model for Trail Making Test Part B in Former Smokers (N=84)

Overall Model: F=3.9 (p=0.002)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Sex** | | | | | | |
| Male | Reference | Reference | | | | |
| **Female** | **4.32** | **0.23** | **0.57** | **8.07** | **1.88** | **0.03** |
| Smoking History (pack-years) | 0.03 | 0.10 | -0.03 | 0.09 | 0.03 | 0.33 |
| Estimated Premorbid IQ (WRAT4) | 0.25 | 0.20 | -0.008 | 0.50 | 0.13 | 0.06 |
| **Severity of Airflow Limitation by GOLD stage** | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| Mild-Moderate (GOLD 1-2) | -3.96 | -0.21 | -8.63 | 0.72 | 2.35 | 0.10 |
| **Severe-Very Severe (GOLD 3-4)** | **-5.20** | **-0.25** | **-10.11** | **-0.30** | **2.46** | **0.04** |
| **Carotid β-Stiffness Index (U)** | **-0.78** | **-0.33** | **-1.29** | **-0.28** | **0.26** | **0.003** |

Note: WRAT4= Wide Range Achievement Test 4;
Dependent variable= Executive functioning-processing speed t-score calculated using age-adjusted normative data (see supplementary Table 2 for norm references)

Table S9. Results of Simultaneous Multiple Linear Regression Model for Controlled Oral Word Association in Former Smokers (N=84)

Overall Model: F=4.0 (p=0.002)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Sex** | | | | | | |
| Male | Reference | Reference | | | | |
| **Female** | **5.65** | **0.30** | **1.93** | **9.36** | **1.87** | **0.003** |
| Smoking History (pack-years) | 0.02 | 0.09 | -0.04 | 0.08 | 0.03 | 0.43 |
| **Estimated Premorbid IQ (WRAT4)** | **0.27** | **0.22** | **0.02** | **0.52** | **0.13** | **0.04** |
| **Severity of Airflow Limitation by GOLD stage** | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| Mild-Moderate (GOLD 1-2) | -2.67 | -0.14 | -7.30 | 1.96 | 2.33 | 0.25 |
| **Severe-Very Severe (GOLD 3-4)** | **-6.78** | **-0.33** | **-11.63** | **-1.92** | **2.44** | **0.007** |
| **Carotid β-Stiffness Index (U)** | **-0.56** | **-0.24** | **-1.06** | **-0.06** | **0.25** | **0.03** |

Note: WRAT4= Wide Range Achievement Test 4;
Dependent variable= Executive functioning-processing speed t-score calculated using age-adjusted normative data (see supplementary Table 2 for norm references)

Table S10. Results of Simultaneous Multiple Linear Regression Model for WAIS-IV Coding in Former Smokers (N=84)

Overall Model: F=3.7 (p=0.003)

| **Independent Variable** | **Unstandardized b** | **Standardized b** | **95% Confidence Interval** | | **SE** | **p** |
|---|---|---|---|---|---|---|
| | | | **Lower Bound** | **Upper Bound** | | |
| **Sex** | | | | | | |
| Male | Reference | Reference | | | | |
| **Female** | **4.95** | **0.32** | **1.83** | **8.07** | **1.57** | **0.002** |
| Smoking History (pack-years) | -0.001 | -0.003 | -0.05 | 0.05 | 0.03 | 0.98 |
| **Estimated Premorbid IQ (WRAT4)** | **0.35** | **0.34** | **0.14** | **0.56** | **0.11** | **0.001** |
| **Severity of Airflow Limitation by GOLD stage** | | | | | | |
| No COPD (GOLD 0- Normal lung CT) | Reference | Reference | | | | |
| Mild-Moderate (GOLD 1-2) | -2.36 | -0.15 | -6.24 | 1.53 | 1.95 | 0.23 |
| **Severe-Very Severe (GOLD 3-4)** | **-4.15** | **-0.24** | **-8.23** | **-0.08** | **2.05** | **0.046** |
| Carotid β-Stiffness Index (U) | 0.001 | 0.001 | -0.42 | 0.42 | 0.21 | 0.996 |

Note: WRAT4= Wide Range Achievement Test 4;
Dependent variable= Executive functioning-processing speed t-score calculated using age-adjusted normative data (see supplementary Table 2 for norm references)