

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Percent Emphysema, Airflow Obstruction and Impaired Left Ventricular Filling

Online Supplementary Appendix

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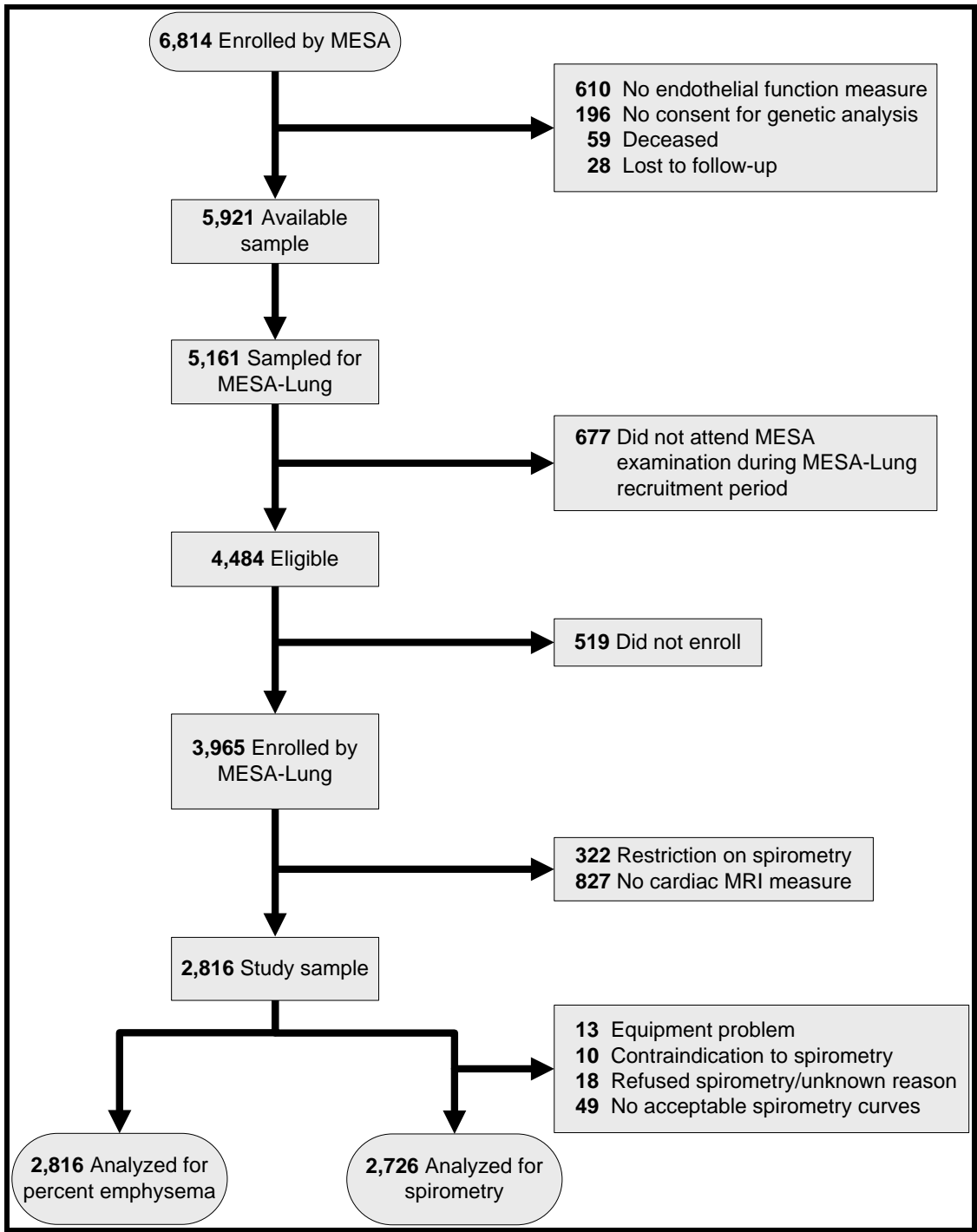
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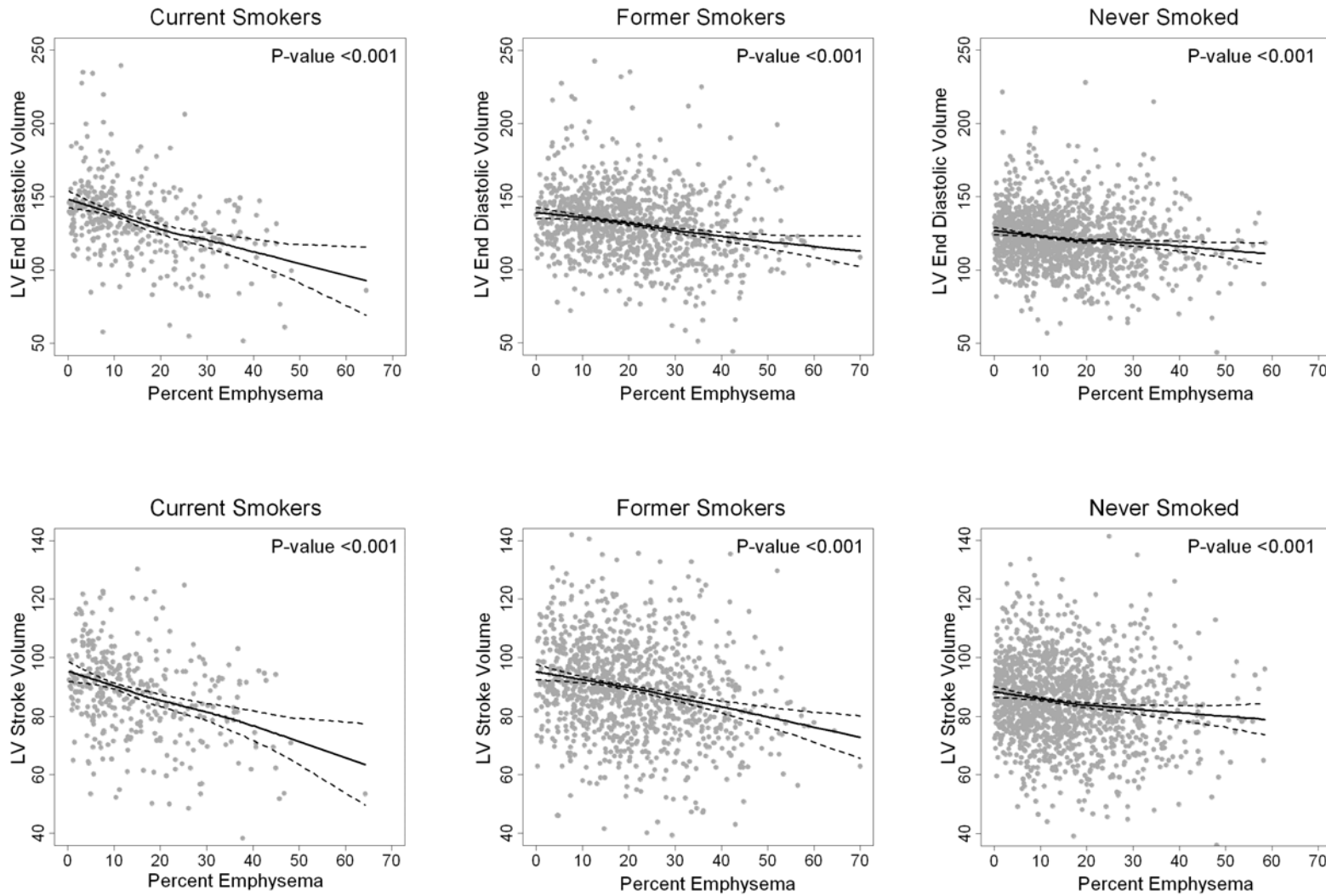
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Online Supplement Figure 1. Flow diagram of participant selection in the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study.



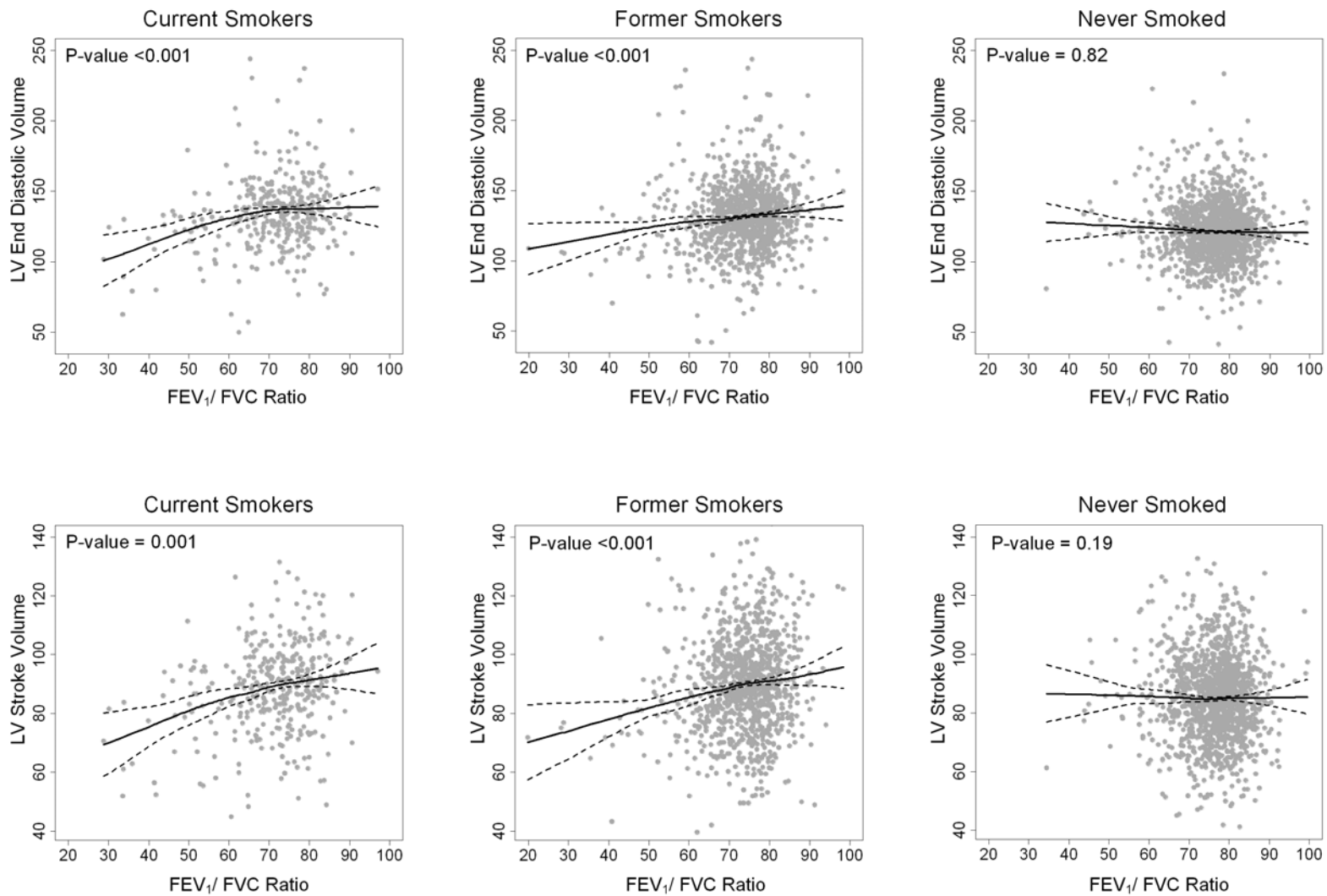
MESA = Multi-Ethnic Study of Atherosclerosis; MRI = Magnetic resonance imaging.

Online Supplement Figure 2. Continuous relationships of the percent emphysema to left ventricular end-diastolic volume and stroke volume in current smokers, past smokers and never smokers.



Multivariate relationships of the percent emphysema to left ventricular end-diastolic volume and stroke volume in current, former and never smokers. Thick lines = smoothed regression lines adjusted for age, race/ethnicity, gender, body surface area, pack-years, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, body mass index, hypertension, systolic and diastolic blood pressure, C-reactive protein, fibrinogen, CT scanner type and mA dose. Thin lines = 95% confidence intervals. Dots = predicted + residual values. The smoothing functions did not improve model fit compared to linear terms for the left ventricular end-diastolic volume (P=0.49, P=0.33 and P=0.18 for current, former and never smokers, respectively) and for the left ventricular stroke volume (P=0.68, P=0.86 and P=0.65, respectively), which implies that no thresholds in the relationships of percent emphysema to left ventricular end-diastolic volume and stroke volume could be demonstrated.

Online Supplement Figure 3. Continuous relationships of the forced expiratory volume in one second / forced vital capacity ratio to left ventricular end-diastolic volume and stroke volume in current smokers, past smokers and never smokers.



Multivariate relationship of the forced expiratory volume in one second / forced vital capacity ratio to left ventricular end-diastolic volume and stroke volume in current, former and never smokers. Thick lines = smoothed regression lines adjusted for age, race/ethnicity, gender, body surface area, pack-years, urine cotinine, educational attainment, height, diabetes mellitus, fasting plasma glucose, hypertension, systolic and diastolic blood pressure, C-reactive protein, and fibrinogen. Thin lines = 95% confidence intervals. Dots = predicted + residual values. The smoothing functions did not improve model fit compared to linear terms for the left ventricular end-diastolic volume (P=0.05, P=0.59 and P=0.46 for current, former and never smokers, respectively) and for the left ventricular stroke volume (P=0.36, P=0.53 and P=0.42, respectively).

Online Supplement Table 1 Characteristics of MESA-Lung participants without a restrictive pattern of spirometry with and without left ventricular measures.

	With LV Measures	Without LV Measures
	N=2816	N=827
Age, mean \pm SD, years	61 \pm 10	63 \pm 10
Male gender, N (%)	1383 (49)	402 (49)
Race/ethnicity, %		
White	1005 (36)	274 (33)
African American	701 (25)	264 (32)
Hispanic	616 (23)	192 (23)
Asian	494 (18)	97 (12)
Educational attainment, %		
No high school degree	440 (16)	167 (20)
High school degree	505 (18)	153 (19)
Some college	762 (27)	251 (35)
College degree	534 (19)	133 (16)
Greater than bachelor's degree	575 (20)	123 (10)
Height, mean \pm SD, cm	166 \pm 10	167 \pm 10
Body surface area, mean \pm SD, m ²	1.84 \pm 0.22	1.90 \pm 0.24
Body mass index, mean \pm SD, kg/m ²	27.4 \pm 4.8	29.7 \pm 6.1
Cigarette smoking status, %		
Never	1379 (49)	338 (41)
Former	1067 (38)	346 (42)

Current	370 (13)	143 (17)
Pack-years of smoking, median	16	19
(IQR)	(6.0, 34)	(7, 37)
Hypertension, %	1001 (36)	356 (43)
Systolic blood pressure, mean \pm SD, mmHg	124 \pm 20	128 \pm 20
Diastolic blood pressure, mean \pm SD, mmHg	72 \pm 10	72 \pm 10
Diabetes mellitus, %	249 (9)	93 (11)
Fasting plasma glucose, median	96 [5.33]	98 [5.44]
(IQR), mg/ 100mL [mmol/L]	(89[4.94], 104[5.77])	(92[5.11], 108[5.99])
C-reactive protein, median	1.6	2.15
(IQR), mg/ L [μ g/L]	(0.7, 3.8)	(0.96, 4.56)
Fibrinogen, median	332[9.76]	343[10.09]
(IQR), mg/100 mL [μ mol/L]	(292[8.59], 382[11.23])	(297[8.73], 393[11.56])
Family history of emphysema, %	120 (4)	42 (5)
Asthma before the age of 45 years, %	202 (7)	84 (10)
MRC-defined chronic bronchitis, %	221 (8)	64 (8)
Obstructive sleep apnea, n (%)	79 (3)	30 (4)
Self-report of COPD, emphysema or chronic bronchitis, n (%)	205 (7)	69 (8)
FEV ₁ percent of predicted, mean \pm SD, %	96.2 \pm 17.1	93.9 \pm 18.6
FEV ₁ /FVC ratio, mean \pm SD, %	74.6 \pm 8.6	74.3 \pm 9.19
Percent emphysema, median	15	13.5
(IQR), %	(7.8, 24.9)	(6.9, 23.4)

SD = Standard deviation; IQR = Interquartile range; MRC = Medical Research Council; FEV₁ =
Forced expiratory volume in one second; FVC = Forced vital capacity; LV = Left ventricle

Online Supplement Table 2. Characteristics of participants stratified by smoking status

	Current Smoker N=370	Past Smoker N=1067	Never Smoked N=1379
Age, mean \pm SD, years	58 \pm 9	62 \pm 10	61 \pm 10
Male gender, N (%)	214 (58)	664 (62)	505 (37)
Race/ethnicity %			
White	115 (31)	479 (45)	411 (30)
African American	138 (37)	265 (25)	298 (22)
Hispanic	86 (23)	212 (20)	318 (23)
Asian	31 (8)	111 (10)	352 (26)
Educational attainment, %			
No high school degree	59 (16)	147 (14)	234 (17)
High school degree	79 (21)	178 (17)	248 (18)
Some college	136 (37)	292 (27)	334 (24)
College degree	47 (13)	207 (19)	280 (20)
Greater than bachelor's degree	49 (13)	243 (23)	283 (20)
Height, mean \pm SD, cm	169 \pm 10	169 \pm 10	164 \pm 10
Body surface area, mean \pm SD	1.89 \pm 0.22	1.89 \pm 0.21	1.79 \pm 0.22
Body mass index, mean \pm SD, kg/m ²	27.5 \pm 4.8	27.7 \pm 4.7	27.2 \pm 4.8
Pack-years of smoking, median (IQR)	24 (10.9, 43.5)	14 (5.0, 31.0)	--
Hypertension, %	111 (30)	396 (37)	494 (36)

Systolic blood pressure, mean \pm SD, mmHg	123 \pm 21	125 \pm 19	123 \pm 19
Diastolic blood pressure, mean \pm SD, mmHg	73 \pm 10	72 \pm 10	71 \pm 10
Diabetes mellitus, %	33 (9)	104 (10)	112 (8)
Fasting plasma glucose, median (IQR), mg/ dL [mmol/L]	95[5.27] (89[4.94], 104[5.77])	96[5.33] (90[5.00], 105[5.83])	95[5.27] (89[4.94], 104[5.77])
C-reactive protein, median (IQR), mg/ L	2.2 (1.0, 4.6)	1.5 (0.7, 3.6)	1.6 (0.7, 3.6)
Fibrinogen, median (IQR), mg/dL [μ mol/L]	340[10.00] (295[8.68], 388[11.41])	326[9.59] (288[8.47], 372[10.94])	335[9.85] (294[8.65], 386[11.35])
Family history of emphysema, %	24 (6)	50 (5)	46 (3)
Asthma before the age of 45 years, %	24 (6)	71 (7)	107 (8)
MRC-defined chronic bronchitis, %	62 (17)	83 (8)	76 (6)
Obstructive sleep apnea, n (%)	14 (4)	30 (3)	35 (2)
Self-report of COPD, emphysema or chronic bronchitis, n (%)	32 (9)	95 (9)	78 (6)

SD = Standard deviation; IQR = Interquartile range; MRC = Medical Research Council

Online Supplement Table 3. Percent emphysema on CT scan, lung function, and cardiac structure and function on magnetic resonance image, stratified by smoking status.

	Current Smoker N=370	Past Smoker N=1067	Never Smoked N=1379
Percent emphysema, median (IQR), %	11.3 (5.9, 21.4)	18.7 (10.6, 29.1)	13.4 (6.7, 22.0)
FEV ₁ percent of predicted,* mean ± SD, %	87.5 ± 18.8	95.4 ± 18.2	98.4 ± 15.6
FVC percent of predicted,* mean ± SD, %	94.0 ± 14.7	98.5 ± 15.5	98.5 ± 14.0
FEV ₁ /FVC ratio, mean ± SD, %	71.2 ± 11.0	73.5 ± 8.7	76.4 ± 7.2
LV end-diastolic volume, mean ± SD, mL	133 ± 35	131 ± 31	122 ± 29
LV end-systolic volume, mean ± SD, mL	46 ± 21	42 ± 17	37 ± 15
LV stroke volume, mean ± SD, mL	88 ± 20	89 ± 20	85 ± 19
LV stroke volume index, † mean ± SD	41.8 ± 7.2	41.8 ± 7.1	41.7 ± 7.3
LV cardiac output, mean ± SD, L/min	5.69 ± 1.48	5.79 ± 1.50	5.68 ± 1.46
LV cardiac index, † mean ± SD,	2.6 ± 0.3	2.6 ± 0.3	2.6 ± 0.3
LV ejection fraction, mean ± SD, %	67 ± 8	68 ± 7	70 ± 7
LV mass, mean ± SD, g	158 ± 42	151 ± 39	134 ± 35

SD = Standard deviation; IQR = Interquartile range; FEV₁ = Forced expiratory volume in one second;

FVC = Forced vital capacity; LV = Left ventricle

* Predicted values calculated from the National Health and Nutrition Survey III reference equations for whites, African-Americans and Hispanics and with a correction factor of 0.88 for Asians.^{12,25}

† Indexed by body surface area

Online Supplement Table 4. Predicted measures of left ventricular structure and function by quintiles of percent emphysema and mean differences per 10 percentage point change in percent emphysema among current, former and never smokers.

	Predicted LV Measure according to Quintile of					Mean Difference in LV Measure	P-value
	Percent Emphysema					(95% CI) per 10 Percentage	
						Point Increase in Percent	
						Emphysema	
<u>Current Smokers (n)</u>	74	74	74	74	74	370	
Median Percent Emphysema, %	3.0	7.1	11.3	19.1	32.5		
LV End-Diastolic Volume, mL	135	129	124	112	107	-9.2	<0.001
						(-11.8, -6.5)	
LV End-Systolic Volume, mL	46	42	41	38	31	-4.4	<0.001
						(-6.2, -2.6)	
LV Stroke Volume, mL	89	87	83	82	76	-4.8	<0.001
						(-6.4, -3.2)	
Cardiac Output, L/min	5.60	5.31	5.14	4.72	4.53	-0.36	<0.001
						(-0.49, -0.24)	

LV Ejection Fraction,%	67	67	68	68	70	0.7	0.053
						(-0.005, 1.5)	
LV Mass, g	161	162	159	160	147	-5.5	<0.001
						(-8.6, -2.5)	
<u>Former Smokers (n)</u>	213	214	214	213	213	1067	
Median Percent Emphysema, %	5.4	12.3	18.7	26.4	38.9		
LV End-Diastolic Volume, mL	129	127	126	119	115	-4.2	<0.001
						(-5.4, -2.8)	
LV End-Systolic Volume, mL	40	39	40	35	35	-1.9	<0.001
						(-2.2, -0.6)	
LV Stroke Volume, mL	89	89	86	84	80	-2.7	<0.001
						(-3.6, -1.9)	
Cardiac Output, L/min	5.95	5.78	5.72	5.64	5.45	-0.14	<0.001
						(-0.21, -0.06)	
LV Ejection Fraction, %	70	70	69	71	70	-0.04	0.85
						(-0.4, 0.3)	

LV Mass, g	146	142	141	139	132	-3.3	<0.001
						(-4.7, -1.9)	
<u>Never Smoked (n)</u>	275	276	277	275	276	1379	
Median Percent Emphysema, %	2.7	7.9	13.4	19.9	31.2		
LV End-Diastolic Volume, mL	120	116	113	113	111	-2.6	<0.001
						(-3.7, -1.4)	
LV End-Systolic Volume, mL	35	33	32	33	32	-0.8	0.01
						(-1.5, -0.2)	
LV Stroke Volume, mL	85	83	81	80	79	-1.8	<0.001
						(-2.6, -0.9)	
Cardiac Output, L/min	5.82	5.66	5.61	5.49	5.18	-0.17	<0.001
						(-0.24, -0.10)	
LV Ejection Fraction, %	72	72	72	72	71	0.1	0.70
						(-0.3, 0.4)	
LV Mass, g	129	127	124	125	125	-0.8	0.22
						(-2.0, 0.4)	

LV = left ventricle

Predicted measures and mean differences adjusted for age, race/ethnicity, gender, body surface area, pack-years, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, body mass index, hypertension, systolic and diastolic blood pressure, C-reactive protein, fibrinogen, CT scanner type and mA dose. Predicted measures and mean differences, along with 95% confidence intervals and P-values for the linear term for percent emphysema, were estimated in generalized additive models.

Online Supplement Table 5. Predicted measures of left ventricular structure and function by quintiles of the FEV₁/FVC ratio and mean differences per 10 percentage point change in the FEV₁/FVC ratio among current, former and never smokers.

	Predicted LV Measure according to Quintile of					Mean Difference in LV Measure (95% CI) per 10 Percentage Point Increase in the FEV ₁ /FVC Ratio	P-value
	the FEV ₁ /FVC Ratio						
<u>Current Smokers (n)</u>	72	72	72	72	71	359	
Median FEV ₁ /FVC Ratio, %	82.7	77.5	73.4	67.5	55.5		
LV End-Diastolic Volume, mL	133	132	129	136	121	5.1 (2.0, 8.2)	0.001
LV End-Systolic Volume, mL	44	43	43	48	41	1.5 (-0.6, 3.5)	0.16
LV Stroke Volume, mL	89	89	86	88	80	3.6 (1.8, 5.4)	<0.001
Cardiac Output, L/min	5.70	5.79	5.68	5.65	5.24	0.19 (0.05, 0.34)	0.01

LV Ejection Fraction,%	67	68	67	66	67	-0.2	0.69
						(-1.0, 0.7)	
LV Mass, g	155	160	157	170	154	0.6	0.71
						(-2.8, 4.0)	
<u>Former Smokers (n)</u>	206	206	206	206	205	1029	
Median FEV ₁ /FVC Ratio, %	82.6	78.2	74.7	70.3	63.4		
LV End-Diastolic Volume, mL	135	132	132	130	127	3.2	<0.001
						(1.3, 5.0)	
LV End-Systolic Volume, mL	42	42	41	40	41	0.3	0.60
						(-0.8, 1.4)	
LV Stroke Volume, mL	93	90	91	90	86	2.9	<0.001
						(1.6, 4.2)	
Cardiac Output, L/min	5.99	5.96	6.00	5.80	5.50	0.17	0.003
						(0.06, 0.28)	
LV Ejection Fraction, %	70	69	70	70	68	0.4	0.17
						(-0.2, 0.9)	

LV Mass, g	156	153	153	151	153	0.2 (-1.8, 2.2)	0.86
<u>Never Smoked (n)</u>	267	268	268	268	267	1338	
Median FEV ₁ /FVC Ratio, %	84.2	80.2	77.3	73.7	67.5		
LV End-Diastolic Volume, mL	120	121	121	119	123	-1.1 (-2.8, 0.5)	0.19
LV End-Systolic Volume, mL	36	36	37	37	38	-1.0 (-19, -0.1)	0.03
LV Stroke Volume, mL	83	85	84	82	85	-0.1 (-1.3, 1.1)	0.82
Cardiac Output, L/min	5.66	5.56	5.48	5.51	5.46	0.07 (-0.03, 0.17)	0.18
LV Ejection Fraction, %	70	71	70	70	70	0.5 (-0.03, 0.9)	0.07
LV Mass, g	135	133	132	134	140	-2.6	0.003

(-4.3, -0.9)

FEV₁ = Forced expiratory volume in one second; FVC = Forced vital capacity; LV = Left ventricle

Predicted measures and mean differences adjusted for age, race/ethnicity, gender and body surface area, pack-years, urine cotinine, educational attainment, height, diabetes mellitus, fasting plasma glucose, hypertension, systolic and diastolic blood pressure, C-reactive protein, and fibrinogen. Predicted measures and mean differences, along with 95% confidence intervals and P-values for the linear term for FEV₁/FVC ratio, were estimated in generalized additive models.

Online Supplement Table 6. Predicted measures of left ventricular structure and function by quintiles of the forced expiratory volume in one second and mean differences per 750 mL increase in forced expiratory volume in one second among current, former and never smokers.

	Quintile of Percent FEV ₁ (mL)					Mean Difference in Left Ventricular Measure (95% CI) by 750 mL (SD) Increase in FEV ₁	P-value
<u>Current Smokers (n)</u>	72	72	72	72	72	360	
Median FEV ₁ , mL	3423	2771	2360	1969	1419		
LV End-Diastolic Volume, mL	134	132	121	120	113	6.8 (2.1, 11.5)	0.005
LV End-Systolic Volume, mL	44	44	39	37	37	2.6 (-0.5, 5.7)	0.10
LV Stroke Volume, mL	90	89	83	83	78	4.2 (1.5, 7.0)	0.003
Cardiac Output, L/min	5.59	5.41	5.54	5.20	5.19	0.16	0.16

						(-0.06, 0.38)	
LV Ejection Fraction,%	68	67	68	70	69	-0.7	0.26
						(-2.0, 0.5)	
LV Mass, g	147	155	146	142	146	0.9	0.75
						(-4.3, 6.0)	
<u>Former Smokers (n)</u>	207	207	207	207	206	1034	
Median FEV ₁ , mL	3547	2954	2518	2131	1641		
LV End-Diastolic Volume, mL	128	122	116	117	113	6.5	<0.001
						(4.1, 9.0)	
LV End-Systolic Volume, mL	38	36	33	34	33	2.5	<0.001
						(1.1, 3.9)	
LV Stroke Volume, mL	90	86	83	83	80	4.0	<0.001
						(2.3, 5.8)	
Cardiac Output, L/min	5.92	5.71	5.47	5.49	5.36	0.19	0.01
						(0.04, 0.33)	
LV Ejection Fraction, %	71	71	72	71	71	-0.3	0.47

						(-1.0, 0.4)	
LV Mass, g	133	133	131	135	134	0.3	0.79
						(-2.2, 2.9)	
<u>Never Smoked (n)</u>	270	269	270	269	269	1347	
Median FEV ₁ , mL	3365	2649	2268	1949	1523		
LV End-Diastolic Volume, mL	106	102	102	102	104	2.3	0.06
						(-0.1, 4.7)	
LV End-Systolic Volume, mL	30	28	27	28	28	0.7	0.31
						(-0.6, 2.0)	
LV Stroke Volume, mL	76	73	74	74	76	1.6	0.07
						(-0.1, 3.3)	
Cardiac Output, L/min	5.17	5.07	5.10	5.01	5.17	0.09	0.23
						(-0.06, 0.24)	
LV Ejection Fraction, %	73	72	73	73	73	0.02	0.96
						(-0.7, 0.7)	
LV Mass, g	118	115	114	116	118	1.4	0.25

(-1.0, 3.9)

FEV₁ = Forced expiratory volume in one second; LV = Left ventricle

Online Supplement Table 7. Mean differences and 95% confidence intervals per 10 percentage point increase in percent emphysema among current, former and never smokers in sensitivity analyses.

	1.	2.	3.	4.	5.	6.	7.
	Controlling for height and weight instead of BSA and BMI	Controlling for height^{2,7} instead of BSA and BMI	Weighted by the probability of MRI completion	Including 322 participants with restriction on spirometry	Controlling for additional covariates**	Controlling for age of smoking initiation/cessation + cigarettes/day instead of pack-years	Excluding 25 participants with subclinical wall motion abnormalities
<u>Current Smokers</u>							
LV End-Diastolic Volume (mL)	-8.8‡ (-11.5, -6.2)	-9.4‡ (-12.2, -6.7)	-9.0‡ (-11.7, -6.4)	-9.3‡ (-11.8, -6.8)	-9.6‡ (-12.3, -6.9)	-8.7‡ (-11.3, -6.0)	-7.8‡ (-10.4, -5.3)
LV End-Systolic Volume (mL)	-4.2‡ (-6.0, -2.5)	-4.4‡ (-6.2, -2.6)	-4.4‡ (-6.2, -2.7)	-4.5‡ (-6.1, -2.8)	-4.6‡ (-6.4, -2.8)	-4.2‡ (-6.0, -2.5)	-3.3‡ (-5.0, -1.7)

LV Stroke Volume (mL)	-4.6‡ (-6.2, -3.0)	-5.1‡ (-6.7, -3.4)	-4.6‡ (-6.2, -3.1)	-4.8‡ (-6.3, -3.3)	-5.0‡ (-6.6, -3.4)	-4.4‡ (-6.0, -2.9)	-4.5‡ (-6.1, -2.9)
LV Cardiac Output (L/min)	-0.34‡ (-0.46, -0.21)	-0.36‡ (-0.49, -0.23)	-0.35‡ (-0.47, -0.22)	-0.35‡ (-0.47, -0.22)	-0.37‡ (-0.50, -0.24)	-0.34‡ (-0.46, -0.22)	-0.34‡ (-0.47, -0.21)
LV Ejection Fraction (%)	0.7 (-0.1, 1.4)	0.7 (-0.1, 1.4)	0.8* (0.03, 1.5)	0.8* (0.1, 1.5)	0.8 (-0.003, 1.5)	0.7 (-0.02, 1.5)	0.4 (-0.3, 1.1)
LV Mass (gm)	-5.3‡ (-8.3, -2.3)	-6.1‡ (-9.3, -3.0)	-5.5‡ (-8.5, -2.5)	-5.0‡ (-7.9, -2.2)	-5.6‡ (-8.8, -2.5)	-4.9‡ (-7.9, -1.9)	-4.6‡ (-7.6, -1.6)

Former Smokers

LV End-Diastolic Volume (mL)	-4.2‡ (-5.5, -2.9)	-5.0‡ (-6.3, -3.7)	-4.2‡ (-5.5, -2.9)	-4.3‡ (-5.6, -3.1)	-4.0‡ (-5.3, -2.8)	-4.1‡ (-5.4, -2.8)	-4.1‡ (-5.4, -2.9)
LV End-Systolic Volume (mL)	-1.4‡ (-2.2, -0.7)	-1.7‡ (-2.5, -0.9)	-1.4‡ (-2.2, -0.6)	-1.6‡ (-2.4, -0.9)	-1.3‡ (-2.1, -0.5)	-1.4‡ (-2.1, -0.6)	-1.4‡ (-2.2, -0.7)
LV Stroke Volume (mL)	-2.8‡ (-3.7, -1.9)	-3.3‡ (-4.2, -2.4)	-2.8‡ (-3.7, -1.9)	-2.7‡ (-3.5, -1.9)	-2.7‡ (-3.6, -1.8)	-2.7‡ (-3.6, -1.9)	-2.7‡ (-3.6, -1.8)
LV Cardiac Output	-0.14‡	-0.17‡	-0.14‡	-0.14‡	-0.13‡	-0.14‡	-0.14‡

(L/min)	(-0.21, -0.06)	(-0.25, -0.10)	(-0.21, -0.06)	(-0.20, -0.07)	(-0.20, -0.05)	(-0.21, -0.06)	(-0.21, -0.06)
LV Ejection Fraction (%)	-0.02	-0.01	-0.04	0.1	-0.1	-0.1	0.0003
	(-0.4, 0.4)	(-0.4, 0.4)	(-0.4, 0.3)	(-0.3, 0.4)	(-0.5, 0.3)	(-0.4, 0.3)	(-0.4, 0.4)
LV Mass (gm)	-3.3‡	-4.6‡	-3.3‡	-3.2‡	-3.4‡	-3.2‡	-3.2‡
	(-4.7, -1.9)	(-6.1, -3.1)	(-4.7, -1.9)	(-4.5, -1.8)	(-4.8, -2.0)	(-4.6, -1.9)	(-4.6, -1.8)
<u>Never Smokers</u>							
LV End-Diastolic Volume	-2.6‡	-4.1‡	-2.7‡	-2.3‡	-2.7‡	-2.6‡	-2.5‡
(mL)	(-3.8, -1.4)	(-5.2, -2.9)	(-3.9, -1.6)	(-3.4, -1.2)	(-3.9, -1.5)	(-3.7, -1.4)	(-3.6, -1.3)
LV End-Systolic Volume	-0.8*	-1.2‡	-0.9†	-0.7*	-0.8*	-0.8*	-0.8*
(mL)	(-1.4, -0.1)	(-1.9, -0.6)	(-1.5, -0.2)	(-1.4, -0.1)	(-1.5, -0.2)	(-1.5, -0.2)	(-1.4, -0.2)
LV Stroke Volume (mL)	-1.8‡	-2.8‡	-1.9‡	-1.6‡	-1.9‡	-1.8‡	-1.7‡
	(-2.7, -1.0)	(-3.7, -2.0)	(-2.7, -1.0)	(-2.4, -0.7)	(-2.7, -1.0)	(-2.6, -0.9)	(-2.5, -0.8)
LV Cardiac Output	-0.17‡	-0.22‡	-0.18‡	-0.15‡	-0.16‡	-0.17‡	-0.17‡
(L/min)	(-0.24, -0.10)	(-0.29, -0.15)	(-0.25, -0.11)	(-0.22, -0.08)	(-0.23, -0.08)	(-0.24, -0.10)	(-0.24, -0.09)
LV Ejection Fraction (%)	0.04	0.05	0.1	0.1	0.1	0.1	0.1
	(-0.3, 0.4)	(-0.3, 0.4)	(-0.3, 0.4)	(-0.3, 0.4)	(-0.3, 0.4)	(-0.3, 0.4)	(-0.3, 0.4)

LV Mass (gm)	-0.9	-3.1‡	-0.8	-0.9	-0.9	-0.8	-0.7
	(-2.1, 0.4)	(-4.4, -1.7)	(-2.0, 0.4)	(-2.1, 0.3)	(-2.1, 0.3)	(-2.0, 0.5)	(-2.0, 0.5)

LV = left ventricle; BMI = body mass index; BSA = body surface area; MRI = magnetic resonance imaging

All analyses adjusted for age, race/ethnicity, gender, body surface area, pack-years, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, body mass index, hypertension, systolic and diastolic blood pressure, C-reactive protein, fibrinogen, CT scanner type and mA dose, except as noted in column headings.

* P-value = 0.01 – 0.05

† P-value = 0.001 – 0.01

‡ P-value < 0.001

**Further adjusted for physical exercise, time before first cigarette in the morning, depth of smoke inhalation, cigar smoking status, cumulative cigar-years, pipe smoking status, cumulative pipe-years, presence of sleep breathing disorder, low density lipoprotein, and high density lipoprotein.

Online Supplement Table 8. Mean differences and 95% confidence intervals per 10 percentage point increase in FEV1/FVC ratio among current, former and never smokers in sensitivity analyses.

	1.	2.	3.	4.	5.	6.	7.
	Controlling for height and weight instead of BSA and BMI	Controlling for height^{2,7} instead of BSA and BMI	Weighted by the probability of MRI completion	Including 322 participants with restriction on spirometry	Controlling for additional covariates**	Controlling for age of smoking initiation/cessation + cigarettes/day instead of pack-years	Excluding 25 participants with subclinical wall motion abnormalities
<u>Current Smokers</u>							
LV End-Diastolic Volume (mL)	4.9† (1.8, 7.9)	6.3‡ (3.2, 9.3)	5.0† (2.0, 8.0)	4.5† (1.6, 7.4)	5.2† (2.0, 8.4)	5.0† (1.9, 8.0)	4.8† (1.9, 7.7)
LV End-Systolic	1.4	1.9	1.5	1.4	1.7	1.3	1.2

Volume (mL)	(-0.6, 3.5)	(-0.1, 3.9)	(-0.5, 3.6)	(-0.5, 3.3)	(-0.5, 3.8)	(-0.7, 3.3)	(-0.6, 3.1)
LV Stroke Volume (mL)	3.5‡ (1.7, 5.3)	4.3‡ (2.5, 6.2)	3.5‡ (1.7, 5.2)	3.1‡ (1.4, 4.8)	3.5‡ (1.7, 5.4)	3.6‡ (1.9, 5.4)	3.6‡ (1.8, 5.3)
LV Cardiac Output (L/min)	0.18* (0.04, 0.32)	0.23† (0.09, 0.38)	0.17† (0.02, 0.31)	0.13 (-0.01, 0.27)	0.19* (0.04, 0.34)	0.19* (0.04, 0.33)	0.19* (0.04, 0.33)
LV Ejection Fraction (%)	-0.2 (-1.0, 0.7)	-0.2 (-1.0, 0.6)	-0.2 (-1.1, 0.6)	-0.3 (-1.1, 0.5)	-0.3 (-1.2, 0.5)	-0.1 (-0.9, 0.8)	-0.1 (-0.9, 0.7)
LV Mass (gm)	0.3 (-3.1, 3.7)	2.4 (-1.1, 5.8)	0.6 (-2.7, 4.0)	0.7 (-2.5, 3.8)	0.7 (-2.8, 4.2)	0.3 (-3.0, 3.6)	0.2 (-3.1, 3.5)

Former Smokers

LV End-Diastolic Volume (mL)	3.2‡ (1.3, 5.0)	3.7‡ (1.8, 5.6)	3.4‡ (1.6, 5.3)	2.9† (1.1, 4.7)	2.9† (1.0, 4.8)	3.2‡ (1.4, 5.1)	2.8† (0.9, 4.6)
LV End-Systolic Volume (mL)	0.3 (-0.8, 1.4)	0.5 (-0.6, 1.6)	0.3 (-0.8, 1.4)	0.4 (-0.7, 1.5)	0.4 (-0.7, 1.5)	0.4 (-0.7, 1.5)	-0.005 (-1.1, 1.1)
LV Stroke Volume (mL)	2.8‡ (1.5, 4.1)	3.2‡ (1.9, 4.5)	3.1‡ (1.8, 4.4)	2.5‡ (1.2, 3.7)	2.5‡ (1.2, 3.8)	2.9‡ (1.6, 4.2)	2.8‡ (1.5, 4.1)

LV Cardiac Output	0.17†	0.20‡	0.18†	0.14†	0.16†	0.16†	0.17†
(L/min)	(0.06, 0.28)	(0.08, 0.31)	(0.07, 0.29)	(0.05, 0.24)	(0.05, 0.27)	(0.05, 0.27)	(0.06, 0.28)
LV Ejection Fraction	0.4	0.4	0.4	0.3	0.3	0.4	0.5
(%)	(-0.2, 0.9)	(-0.2, 0.9)	(-0.1, 1.0)	(-0.2, 0.8)	(-0.3, 0.8)	(-0.2, 0.9)	(-0.03, 1.0)
LV Mass (gm)	0.2	0.9	0.2	0.8	0.5	0.4	-0.3
	(-1.8, 2.1)	(-1.2, 3.0)	(-1.7, 2.2)	(-1.0, 2.7)	(-1.5, 2.4)	(-1.6, 2.3)	(-2.2, 1.7)

Never Smokers

LV End-Diastolic	-1.2	-0.1	-1.2	-1.2	-0.9	-1.1	-0.7
Volume (mL)	(-2.8, -6.7)	(-1.9, -3.9)	(-2.8, -6.7)	(-2.9, -6.8)	(-2.6, -5.9)	(-2.8, -6.6)	(-2.4, -5.4)
LV End-Systolic	-1.0*	-0.7	-1.0*	-1.1*	-0.9*	-1.0*	-0.7
Volume (mL)	(-1.9, -0.1)	(-1.6, 0.2)	(-1.9, -0.1)	(-1.9, -0.2)	(-1.8, -0.04)	(-1.9, -0.1)	(-1.6, 0.1)
LV Stroke Volume	-0.1	0.6	-0.1	-0.2	0.1	-0.1	-0.01
(mL)	(-1.3, 1.1)	(-0.7, 1.8)	(-1.3, 1.1)	(-1.3, 1.0)	(-1.1, 1.3)	(-1.3, 1.1)	(-1.2, 1.2)
LV Cardiac Output	0.07	0.11‡	0.08	0.06	0.09	0.07	0.09
(L/min)	(-0.04, 0.17)	(0.004, 0.21)	(-0.03, 0.18)	(-0.04, 0.16)	(-0.02, 0.19)	(-0.03, 0.17)	(-0.02, 0.19)
LV Ejection Fraction	0.5	0.4	0.5	0.48	0.5	0.5	0.4

(%)	(-0.03, 0.9)	(-0.04, 0.9)	(0.01, 1.0)	(0.001, 0.97)	(-0.01, 1.0)	(-0.03, 0.9)	(-0.1, 0.9)
LV Mass (gm)	-2.6†	-1.2	-2.6†	-2.6†	-2.4†	-2.6†	-2.5†
	(-4.3, -0.9)	(-3.1, 0.7)	(-4.3, -0.9)	(-4.2, -0.9)	(-4.2, -0.7)	(-4.3, -0.9)	(-4.2, -0.8)

LV = left ventricle; BMI = body mass index; BSA = body surface area; MRI = magnetic resonance imaging

All analyses adjusted for age, race/ethnicity, gender, body surface area, height, pack-years, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, body mass index, hypertension, systolic and diastolic blood pressure, C-reactive protein and fibrinogen, except as noted in column headings.

* P-value = 0.01 – 0.05

† P-value = 0.001 – 0.01

‡ P-value < 0.001

**Further adjusted for physical exercise, time before first cigarette in the morning, depth of smoke inhalation, cigar smoking status, cumulative cigar-years, pipe smoking status, cumulative pipe-years, presence of sleep breathing disorder, low density lipoprotein, and high density lipoprotein.

Online Supplement Table 9. Mean differences and 95% confidence intervals per 10 percentage point increase in percent emphysema among current, former and never smokers in CT-scan related sensitivity analyses.

	1.	2.	3.	4.
	Percent	Percent	Percent	Percent
	emphysema	emphysema	emphysema	emphysema
	defined at a	defined at a	defined at a	defined at a
	threshold of	threshold of	threshold of	threshold of
	-950 Hounsfield	-910 Hounsfield	-910 Hounsfield	-950 Hounsfield
	units	units corrected	units corrected	units corrected
		for variation in	for variation in	for variation in
		attenuation of	attenuation of	attenuation of
		air outside the	air in the	air in the
		body	trachea	trachea
<u>Current Smokers</u>				
LV End-Diastolic Volume (mL)	-27.3‡ (-36.7, -17.8)	-7.5‡ (-9.9, -5.0)	-6.4‡ (-8.7, -4.1)	-12.1‡ (-17.8, -6.3)
LV End-Systolic Volume (mL)	-11.4‡ (-17.7, -5.1)	-3.6‡ (-5.2, -2.0)	-2.9‡ (-4.4, -1.3)	-4.6* (-8.4, -0.8)
LV Stroke Volume (mL)	-15.8‡ (-21.4, -10.2)	-3.9‡ (-5.3, -2.4)	-3.5‡ (-4.9, -2.1)	-7.5‡ (-10.9, -4.1)
LV Cardiac Output (L/min)	-1.07‡ (-1.51, -0.63)	-0.30‡ (-0.41, -0.19)	-0.25‡ (-0.36, -0.14)	-0.48‡ (-0.75, -0.21)

LV Ejection Fraction (%)	0.8 (-1.8, 3.5)	0.6 (-0.1, 1.2)	0.4 (-0.3, 1.0)	0.2 (-1.4, 1.8)
LV Mass (gm)	-11.3* (-22.1, -0.5)	-3.8† (-6.6, -1.0)	-3.4* (-6.1, -0.8)	-3.6 (-10.1, 2.8)
<u>Former Smokers</u>				
LV End-Diastolic Volume (mL)	-13.3‡ (-18.1, -8.5)	-3.7‡ (-4.8, -2.5)	-3.0‡ (-4.1, -1.9)	-4.5† (-7.4, -1.7)
LV End-Systolic Volume (mL)	-3.4* (-6.3, -0.5)	-1.1† (-1.8, -0.4)	-0.9† (-1.6, -0.2)	-0.6 (-2.3, 1.1)
LV Stroke Volume (mL)	-9.9‡ (-13.3, -6.6)	-2.5‡ (-3.3, -1.7)	-2.1‡ (-2.9, -1.3)	-3.9‡ (-5.9, -1.9)
LV Cardiac Output (L/min)	-0.49‡ (-0.77, -0.20)	-0.13‡ (-0.20, -0.06)	-0.10† (-0.17, -0.03)	-0.19* (-0.36, -0.03)
LV Ejection Fraction (%)	-0.7 (-2.1, 0.7)	-0.1 (-0.4, 0.3)	-0.04 (-0.4, 0.3)	-0.5 (-1.3, 0.4)
LV Mass (gm)	-6.8* (-12.1, -1.5)	-2.8‡ (-4.1, -1.6)	-2.3‡ (-3.5, -1.1)	-1.3 (-4.4, 1.8)
<u>Never Smokers</u>				
LV End-Diastolic Volume (mL)	-7.6† (-12.8, -2.3)	-2.3‡ (-3.3, -1.3)	-2.2‡ (-3.2, -1.3)	-3.9† (-6.7, -1.1)
LV End-Systolic Volume (mL)	-2.1 (-5.0, 0.8)	-0.8† (-1.3, -0.2)	-1.0‡ (-1.5, -0.4)	-1.9* (-3.4, -0.4)
LV Stroke Volume (mL)	-5.5†	-1.5‡	-1.3‡	-2.0*

	(-9.3, -1.6)	(-2.2, -0.8)	(-2.0, -0.6)	(-4.0, -0.004)
LV Cardiac Output (L/min)	-0.58‡	-0.14‡	-0.13‡	-0.25†
	(-0.90, -0.25)	(-0.20, -0.07)	(-0.19, -0.07)	(-0.42, -0.08)
LV Ejection Fraction (%)	0.1	0.1	0.2	0.6
	(-1.5, 1.7)	(-0.2, 0.4)	(-0.1, 0.5)	(-0.2, 1.4)
LV Mass (gm)	1.6	-0.5	-0.6	-0.02
	(-4.0, 7.2)	(-1.5, 0.6)	(-1.6, 0.5)	(-3.0, 2.9)

LV = left ventricle

All analyses adjusted for age, race/ethnicity, gender, body surface area, pack-years, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, body mass index, hypertension, systolic and diastolic blood pressure, C-reactive protein, fibrinogen, CT scanner type and mA dose.

* P-value = 0.01 – 0.05

† P-value = 0.001 – 0.01

‡ P-value < 0.001