Identification of Chronic Obstructive Pulmonary Disease in Lung Cancer Screening Computed Tomographic Scans

Onno M. Mets, MD
Constantinus F. M. Buckens, MD
Pieter Zanen, MD, PhD
Ivana Isgum, PhD
Bram van Ginneken, PhD
Mathias Prokop, MD, PhD
Hester A. Gietema, MD, PhD
Jan-Willem J. Lammers, MD, PhD
Rozemarijn Vliegenthart, MD, PhD
Matthijs Oudkerk, MD, PhD
Rob J. van Klaveren, MD, PhD
Harry J. de Koning, MD, PhD
Willem P. Th. M. Mali, MD, PhD
Pim A. de Jong, MD, PhD

Context Smoking is a major risk factor for both cancer and chronic obstructive pulmonary disease (COPD). Computed tomography (CT)–based lung cancer screening may provide an opportunity to detect additional individuals with COPD at an early stage.

Objective To determine whether low-dose lung cancer screening CT scans can be used to identify participants with COPD.

Design, Setting, and Patients Single-center prospective cross-sectional study within an ongoing lung cancer screening trial. Prebronchodilator pulmonary function testing with inspiratory and expiratory CT on the same day was obtained from 1140 male participants between July 2007 and September 2008. Computed tomographic emphysema was defined as percentage of voxels less than –950 Hounsfield units (HU), and CT air trapping was defined as the expiratory:inspiratory ratio of mean lung density. Chronic obstructive pulmonary disease was defined as the ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) of less than 70%. Logistic regression was used to develop a diagnostic prediction model for airflow limitation.

Main Outcome Measures Diagnostic accuracy of COPD diagnosis using pulmonary function tests as the reference standard.

Results Four hundred thirty-seven participants (38%) had COPD according to lung function testing. A diagnostic model with CT emphysema, CT air trapping, body mass index, pack-years, and smoking status corrected for overoptimism (internal validation) yielded an area under the receiver operating characteristic curve of 0.83 (95% CI, 0.81-0.86). Using the point of optimal accuracy, the model identified 274 participants with COPD with 85 false-positives, a sensitivity of 63% (95% CI, 58%-67%), specificity of 88% (95% CI, 85%-90%), positive predictive value of 76% (95% CI, 72%-81%); and negative predictive value of 79% (95% CI, 76%-82%). The diagnostic model showed an area under the receiver operating characteristic curve of 0.87 (95% CI, 0.86-0.88) for participants with symptoms and 0.78 (95% CI, 0.76-0.80) for those without symptoms.

Conclusion Among men who are current and former heavy smokers, low-dose inspiratory and expiratory CT scans obtained for lung cancer screening can identify participants with COPD, with a sensitivity of 63% and a specificity of 88%.

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SMOKING IS ANNUALLY PROjected to cause more than 8 million deaths worldwide in the coming decades.[1,2] Besides cardiovascular disease and cancer, chronic obstructive pulmonary disease (COPD) is a major cause of death in heavy smokers. Nevertheless, COPD is substantially underdiagnosed.[3,4] Despite a decrease in cardiovascular mortality and stabilization of cancer mortality worldwide, mortality from COPD is increasing.[5] The onset of COPD can be insidious, but the disease can progress to advanced stages with functional disabilities, repeated exacerbations, and early death.[6] Early cessation of smok-

Author Video Interview available at www.jama.com.

Author Affiliations: Department of Radiology (Drs Mets, Prokop, Gietema, Mali, and de Jong), Julius Center for Health Sciences and Primary Care (Dr Buckens), Department of Pulmonology (Drs Zanen and Lammers), and Image Sciences Institute (Drs Isgum and van Ginneken), University Medical Center Utrecht, Utrecht; Diagnostic Image Analysis Group (Dr van Ginneken) and Department of Radiology (Dr Prokop), Radboud University Nijmegen Medical Centre, Nijmegen; Department of Radiology, University Medical Center Groningen, Groningen (Drs Vliegenthart and Oudkerk); Department of Pulmonology, Lievensberg Ziekenhuis, Bergen op Zoom (Dr van Klaveren); and Department of Public Health, Erasmus Medical Center, Rotterdam (Dr de Koning), the Netherlands.
Corresponding Author: Onno M. Mets, MD, Department of Radiology, University Medical Center Utrecht, Heidelberglaan 100, Postbus 85500, 3508GA Utrecht, the Netherlands (o.m.mets@umcutrecht.nl).

ing can prevent disease progression,[7,8] and there is suggestive evidence that early intensive intervention can improve outcomes for patients with COPD.[9] This underlines the importance of early detection of disease.

Modern computed tomography (CT) allows rapid in vivo evaluation of emphysematous parenchymal destruction and small airways dysfunction. Air trapping assessment using chest CT has become established as a technique to quantify small airways dysfunction.[10,11] This allows information on COPD-related changes to be obtained from CT studies performed for other reasons, such as lung cancer screening.

We hypothesized that CT-based lung cancer screening in heavy smokers could provide an opportunity to acquire information on the presence of COPD, without the need for obtaining pulmonary function testing. We analyzed data from a cohort of current and former heavy smokers participating in an ongoing lung cancer screening trial, who underwent inspiratory and expiratory CT scanning and pulmonary function testing.

METHODS

Study Population

This study of COPD was an ancillary study of the Dutch and Belgian Lung Cancer Screening Trial (International Standard Randomised Controlled Trial number ISRCTN63545820).[12] For this study, expiratory CT scans were added to the lung cancer screening protocol at a single center, and CT scanning and pulmonary function testing were performed on the same day and were conducted between July 2007 and September 2008.

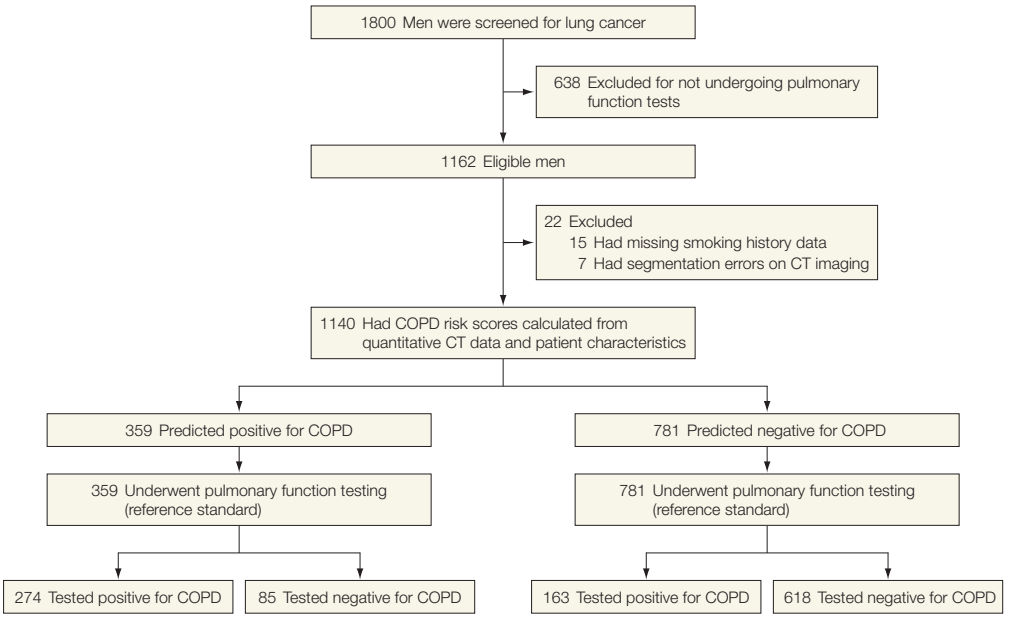
Thus, the study population consisted of men with both CT and pulmonary function testing data and was a subsample of the total group of trial participants who underwent radiological screening for lung cancer. Seven participants with CT segmentation errors and 15 with missing data on smoking habits were excluded (FIGURE 1). Baseline characteristics—age, body mass index, smoking history, and self-reported presence of respiratory symptoms and physician-diagnosed emphysema or bronchitis (eAppendix available at http://www.jama.com)—were collected from all participants in the lung cancer screening trial. Screening trial participants included current or former (<10 years) heavy smokers between the ages of 50 and 75 years with a smoking history of at least 16 cigarettes per day for 25 years or at least 11 cigarettes per day for 30 years (ie, >16.5 pack-years). Exclusion criteria for participating in the lung cancer screening trial were self-reported moderate or poor health with inability to climb 2 flights of stairs, a recent CT scan of the thorax, current or previous history of cancer, and a body weight greater than or equal to 140 kg.[12]

The study was approved by the Dutch and Belgian Ministry of Health and by the ethical review board of the University Medical Center Utrecht. Written informed consent was obtained from each participant.

CT Scanning and Analysis

Low-dose volume scans were acquired after standardized breathing instructions in inspiration and at end expiration. All scans were acquired with 16×0.75 mm collimation (Brilliance 16P; Philips Medical Systems). Set-

Figure 1. Flow Diagram of the Study



COPD indicates chronic obstructive pulmonary disease; CT, computed tomography.

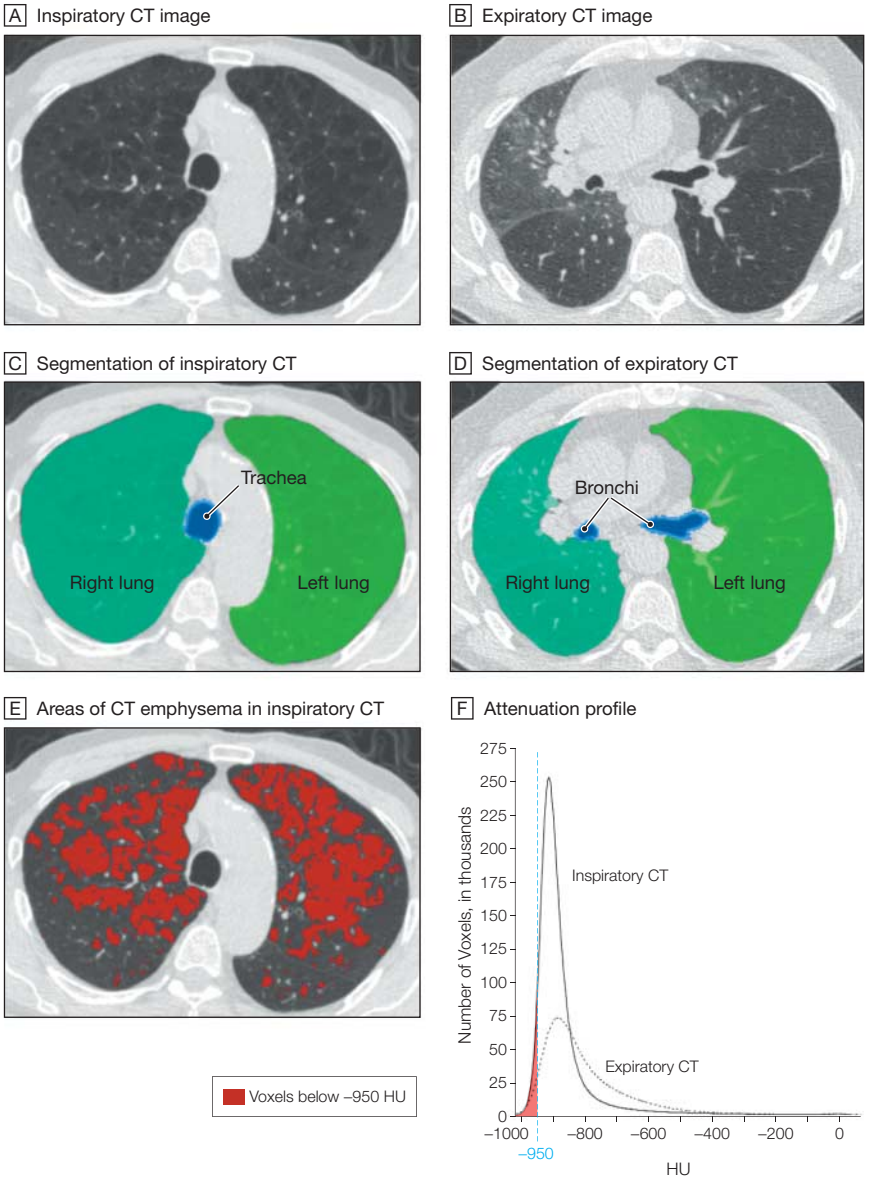
tings were adjusted to body weight: 120 kilovolt (peak) kV(p) for those weighing 80 kg or less or 140 kV(p) for those weighing more than 80 kg, both at 30 mA for inspiratory scans, and 90 kV(p) for those weighing 80 kg or less or 120 kV(p) for those weighing more than 80 kg, both at 20 mA for expiratory scans. A scan pair yielded an estimated effective dose of 1.2 to 2.0 millisievert (mSv), of which 0.3 to 0.65 mSv is accounted for by the expiration scan. Images with section thickness of 1.0 mm at 0.7-mm increments were reconstructed from lung bases to lung apices using a smooth reconstruction kernel (B-filter, Philips).

The lung images were automatically segmented (separated from the chest wall, diaphram, mediastinum, and airways),[13] and a noise reduction filter was applied to decrease the influence of noise on the quantitative measurements.[14] Within the segmented lung volume, the attenuation measured by the Hounsfield units (HU) of each voxel was assessed to quantify emphysema and air trapping severity. Computed tomographic emphysema was defined as the percentage of voxels in inspiratory CT with an attenuation below –950 HU.[15] The HU value at the 15th percentile of the attenuation distribution curve as a measure of CT emphysema[16] was calculated for secondary analysis. Computed tomographic air trapping was defined as the expiratory: inspiratory ratio of mean lung density.[11,17] FIGURE 2 illustrates the quantitative assessment of CT emphysema and CT air trapping.

Pulmonary Function Testing

Prebronchodilator spirometry was performed with ZAN equipment (ZAN messgeräte GmbH), according to European Respiratory Society guidelines.[18] Forced expiratory volume in the first second (FEV_1) was expressed as percent predicted,[19] and the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) was expressed as percentage. Chronic obstructive pulmonary disease was defined as an FEV_1/FVC ratio less than 70% and classified as mild obstruction if the FEV_1 was 80% or higher than predicted, moderate obstruction if the FEV_1 was 50% or higher and less than 80% of predicted, and severe obstruction if the FEV_1 was less than 50% of predicted.[6]

Figure 2. Quantitative Assessment of Computed Tomographic Emphysema and Air Trapping



The figure illustrates the computed tomographic (CT) quantification process. A, Inspiratory CT scan with centrilobular emphysema, seen as areas of hypoattenuation. B, Expiratory CT scan with air trapping, seen as sharply demarcated areas of hypoattenuation in the lung. C and D, In the first step of the quantification process, the lungs, trachea, and main bronchi are segmented. The segmentation process is illustrated using colored overlays for the right (aqua) and left (green) lung, as well as for the trachea and main bronchi (blue). E, The attenuation value of all voxels in the segmented lung volume is calculated. F, The attenuation profiles of the inspiratory and expiratory CT scan are presented in a histogram. Note that when the patient exhales, the histogram shifts to the right (ie, higher attenuation of the voxels) and broadens. Computed tomographic emphysema and CT air trapping are calculated from these attenuation profiles; CT emphysema is defined as a percentage of voxels below –950 Hounsfield units (HU) in inspiratory CT, which is highlighted in red in panel E. The highlighted voxels correspond to the emphysematous areas in panel A. Computed tomographic air trapping is defined as the ratio of expiratory mean lung density over the inspiratory mean lung density. (see eFigures 1 and 2 at http://www.jama.com for additional explanation.)

Table 1. Characteristics of the 1140 Study Participants

Characteristic	Values
Age, mean (SD), y	62.5 (5.2)
BMI, mean (SD)	27.1 (3.6)
Pack-years, median (25th-75th percentile)	38 (28-49)
Smoking status, No. (%)	
Current smokers	609 (53.4)
COPD	262 (43.0)
Former smokers	531 (46.6)
COPD	175 (33.0)
Pulmonary function, mean (SD)	
FEV_1, L	3.2 (0.7)
FEV_1, % predicted	94.8 (17.6)
FEV_1/FVC, %	70.9 (9.3)
COPD No. (%)[a]	437 (38.3)
Severity	
Mild[b]	277 (63.4)
Moderate[c]	135 (30.9)
Severe[d]	25 (5.7)
Respiratory symptoms[e]	
Symptomatic	566 (49.6)
COPD	256 (45.2)
Asymptomatic	519 (45.5)
COPD	160 (30.8)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; COPD, chronic obstructive pulmonary disease; FCV, forced vital capacity FEV_1, forced expiratory volume in the first second.
[a] COPD is defined as an FEV_1/FVC ratio of less than 70%.
[b] An FEV_1/FVC ratio of less than 70% and FEV_1 (% predicted) of more than 80%.
[c] An FEV_1/FVC ratio of less than 70% and FEV_1 (% predicted) 51% to 80%.
[d] An FEV_1/FVC ratio of less than 70% and FEV_1 (% predicted) 31% to 50%.
[e] Data for respiratory symptoms are missing in 55 cases.

Statistical Analysis

Logistic regression was used to develop a multivariable model with the FEV_1/FVC ratio of less than 70% as the outcome, and CT emphysema, CT air trapping, age, body mass index, pack-years of smoking history, and smoking status as possible associated factors. A post hoc power calculation estimated the actual power for developing the diagnostic model given the number of determinants in the model to be 100% for an effective sample size of 437 participants with COPD.[20]

Computed tomographic emphysema measures were transformed using natural logarithm to obtain normal distribution; the other variables did not have to be transformed. The selected full model was simplified based on Akaike information criterion (AIC) in backward fashion.[21] A bootstrap resampling[22,23] procedure using 500 iterations was used to assess the degree of overoptimism in the model (ie, internal validation). The initially estimated coefficients were shrunk by the estimated degree of overoptimism[24] —in which models of derivations studies commonly fit too well to the study sample limiting the application to external populations—so the model intercept was reestimated accordingly. For the shrunk model, calibration was assessed visually in a calibration plot and discrimination was evaluated using a receiver operating characteristic (ROC) curve. Subsequently, the area under the curve (C statistic) was calculated. The model provided a risk score for COPD, varying between 0 and 1. Several points on the ROC curve (ie, risk scores) were considered as cut points, and sensitivity and specificity were calculated. The point of optimal accuracy was defined as the cut-point value with the highest number of true-positive results from the model plus true-negative patients.

Separate analyses were performed to evaluate the change in the model performance when different quantitative CT measures of emphysema alone or together with air trapping were added stepwise to a baseline model that included only clinical data (eTable 1).We also assessed the performance of the model to predict COPD in symptomatic and asymptomatic participants separately. (We defined symptomatic patients as those who reported presence or absence of cough, sputum production, dyspnea, and wheezing.) For this analysis, we imputed missing data on respiratory symptoms in 55 cases (4.8%) using multiple imputation technique.

$P < .05$ was considered statistically significant with 2-sided hypothesis testing. Data analyses were performed with R statistical program (v.2.13.1) using regression modeling strategies version 3.3-0[22] and ROCR v1.0-4.[25] Data are reported as mean (SD), unless indicated otherwise.

RESULTS

Study Participant Characteristics

Of the 1800 men screened for lung cancer, 1140 who underwent spirometry on the same day represent our subsample (Figure 1). There were no important clinical differences between the subsample of participants who underwent pulmonary function testing and those who did not (eTable 2).

The mean (SD) age of participants was 62.5 (5.2) years (TABLE 1). Current and former smokers were roughly equally represented. Data for self-reported respiratory symptoms were available from 1085 participants; a total of 566 participants were symptomatic, and 519 participants were asymptomatic. Forty-one participants (3.6%) reported physician-diagnosed emphysema and 93 (8.2%), bronchitis. Based on the results of pulmonary function testing, 437 participants (38%) had COPD.

Diagnostic Model for Obstructive Pulmonary Disease

The final model included 5 factors independently associated with obstructive pulmonary disease: CT emphysema, CT air trapping, BMI, pack-years, and smoking status (TABLE 2). Age was excluded from the initial model because it did not contribute significantly. The degree of overoptimism corrected for by shrinking the coefficients was small: 0.0224 (2%). Visual inspection of the calibration plot showed excellent agreement across the entire range of predicted risks for obstructive disease (eFigure 1). The discrimination of the final model, after bootstrap shrinkage, was good with a C statistic of 0.83 (95% CI, 0.81-0.86). Discrimination for symptomatic participants was 0.87 (95% CI, 0.86-0.88) and was 0.78 (95% CI, 0.76-0.80) for asymptomatic participants. Model fitting for each of these subgroups separately, or adding symptoms as a predictor to the model, did

Table 2. Independent Predictors of Chronic Obstructive Pulmonary Disease in Lung Cancer Screening Trial Participants[a]

	Constant	CT Emphysema, %[b]	CT Air Trapping, %[c]	Body Mass Index[d]	Pack-Years	Former Smoker
OR (95% CI)		2.47 (2.09 to 2.92)	1.16 (1.13 to 1.20)	0.94 (0.90 to 0.98)	1.01 (1.00 to 1.02)	0.49 (0.36 to 0.69)
β (95% CI)	−11.40 (−14.22 to −8.582)	0.904 (0.737 to 1.070)	0.152 (0.122 to 0.181)	−0.065 (−1.077 to −0.021)	0.008 (0.002 to 0.016)	−0.711 (−1.019 to −0.403)
P Value	<.001	<.001	<.001	.003	.04	<.001

Abbreviations: β, logistic regression coefficient; OR, odds ratio.
[a]The variables included in the logistic regression analysis are $logIN_{-950}$, $E/I\text{-}ratio_{MLD}$, body mass index, pack-years of smoking history, and smoking status.
[b]$logIN_{-950}$, log-transformed percentage of total lung volume below threshold of −950 HU.
[c]$E/I\text{-}ratio_{MLD}$, expiratory to inspiratory ratio of mean lung density.
[d]Calculated as weight in kilograms divided by height in meters squared.

not further increase the performance compared with the overall model, with C statistics ranging from 0.78 (95% CI, 0.76-0.80) to 0.87 (95% CI, 0.86-0.88).

The optimum cut point for accuracy on the ROC curve (FIGURE 3) represented a sensitivity of 62.7% (95% CI, 58.1%-67.1%) and a specificity of 87.9% (95% CI, 85.3%-90.1). Based on this optimum cut point, which is 78% accurate, 359 of 1140 screening participants were categorized as having COPD, which was confirmed in 274 of these participants (positive predictive value, 76% [95% CI, 72%-81%]), which corresponds to 63% (274 of 437) of all participants with COPD. The negative predictive value was 79% (95% CI, 76%-82%). These 274 participants comprised 54% (150 of 277) of all participants with mild obstruction, 73% (99 of 135) of all participants with moderate obstruction, and 100% (25 of 25) of all participants with severe obstruction. Other points on the ROC curve also were considered as cut points (eTable 3 available at http://www.jama.com), but the optimal accuracy point was judged to deliver the most feasible results for lung cancer screening, based on the lowest number of pulmonary function testing performed with acceptable performance measures. Regression equations are presented in the (eEquation).

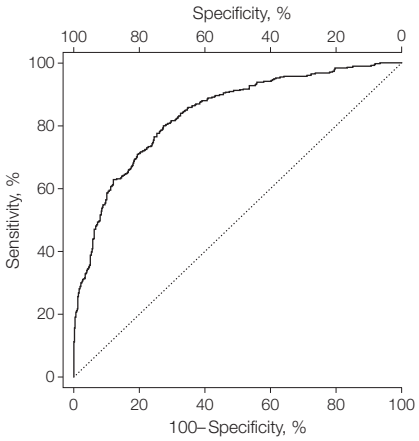
COMMENT

In this study, use of automated analysis of unenhanced low-dose CT scans performed in men undergoing lung cancer screening identified a substantial proportion of participants with COPD. Among 1140 participants screened for lung cancer, 274 of 437 participants (63%) were diagnosed with COPD, with 85 false-positives. Most of these were newly diagnosed COPD cases, given the low prevalence of diagnosed COPD. In subanalyses, COPD was predicted more accurately in symptomatic than in asymptomatic participants, which is likely explained by the presence of more advanced disease in symptomatic patients. However, fitting of separate models for symptomatic and asymptomatic participants did not improve results. If CT screening is widely adopted for lung cancer screening, an additional benefit may be early detection of COPD. Early diagnosis is important because smoking cessation early in the COPD disease process slows disease progression and decreases morbidity and mortality.[3,9]

The results of the National Lung Screening Trial[26] have sparked discussions about implementing[27,28] CT screening for patients who are heavy smokers. Our study may add to the debate about whether and how to implement lung cancer screening for heavy smokers because we have shown that detection of COPD using low-dose screening CT scans may be feasible. Because smokers die not only from lung cancer but also from COPD and cardiovascular disease, the rationale for evaluating lung cancer screening CT scans for additional information may prove important.

Our study findings suggest several practical considerations. If the results of this study are validated and confirmed and are found to be generalizable, it may be reasonable to consider adding an expiratory CT scan to the (baseline) inspiratory CT scan for additional evaluation of COPD because this would improve diagnostic accuracy. Although an additional ultralow–dose expiration CT scan increases the radiation dose, this exposure is limited (0.3-0.65 mSv vs ≈3 mSv of annual background radiation in the United States).[29] The additional scan can be obtained within the 5 minutes needed for lung cancer screening, so a substantial amount of extra scan time is not required.

Figure 3. Receiver Operating Characteristic Curve for the Chronic Obstructive Pulmonary Disease Prediction Model.



The chronic obstructive pulmonary disease (COPD) reference standard for this study was defined as airflow limitation, forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) ratio of less than 70%. The area under the curve for the final model, based on computed tomographic emphysema and air trapping, body mass index, smoking status, and pack-years smoked with COPD as a reference standard is 0.83. The dotted diagonal line represents no discrimination.

However, this possible strategy of using quantitative CT for detection of airflow limitation is not proposed as a primary screening method for COPD, for which pulmonary function testing is the preferred method. A screening test should have a high sensitivity to identify most of the participants with unsuspected disease, and the performance of our strategy at optimal accuracy is not sufficient for CT to serve as a COPD screening test. By lowering the cut point, the sensitivity can be increased; however, this means that more pulmonary function testing will be performed and the positive predictive value would decrease.

The strengths of our study include a relatively large study sample; relatively simple determinants used in our model (ie, body mass index, smoking history, and smoking status can easily be obtained at the screening visit); and CT measures that are relatively simple measures of lung densitometry. We used the accepted quantification methods of a threshold at –950 HU in inspiratory CT, and the 15th percentile of the attenuation distribution curve in inspiratory CT to assess emphysema (the latter performed slightly worse in our analysis), and the ratio of the mean lung attenuation in the expiratory and inspiratory CT scan to assess air trapping. With these densitometry measures, we were able to reasonably identify participants with COPD.

Our study has several limitations. First, external validation in an independent cohort is necessary, and at present our model cannot be widely implemented. Second, the generalizability of our study cohort is limited. The characteristics of participants in this screening study may be different from the characteristics of patients in clinical settings. Also, CT scanning protocols (ie, radiation dose, use of intravascular contrast material, and type of scanner) may differ from those in other screening studies. Attention must be paid to these differences when interpreting and applying our findings. Third, spirometry was not obtained after bronchodilator administration due to time restrictions during screening. Therefore, reversibility in airflow limitation, which is a criterion to exclude asthma in diagnosing COPD, was not assessed.[6,30] However, our results might not be significantly influenced by this limitation. Asthma, whether or not it coexists with COPD, generally involves only a small number of heavily smoking participants. Our study population was population-based, and the prevalence of asthma in men between the ages of 50 and 75 years is approximately 2% in the Netherlands.[31] Fourth, it is possible that some individuals detected by our model were already diagnosed with COPD prior to screening. However, given that patients with more advanced stages were not included due to the exclusion criteria of the screening trial and given that COPD is a substantially underdiagnosed disease in its early stages,[3,4] it is likely that detected individuals represent newly diagnosed cases.

In conclusion, this study shows that quantitative measures in low-dose CT scans may be useful in a lung cancer screening setting to identify heavy smokers with COPD, although external validation is needed before this approach should be considered for implementation. Early intervention may prevent morbidity and mortality from COPD, and because early stages of the disease are substantially underdiagnosed, detection of airflow limitation may provide additional benefit to chest CT-based screening programs involving heavy smokers.

Author Contributions: Dr de Jong had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mets, Buckens, Zanen, Isgum, Ginneken, Prokop, Gietema, Lammers, Vliegenthart, Oudkerk, Klaveren, Koning, Mali, de Jong.
Acquisition of data: Mets, Buckens, Zanen, Isgum, Ginneken, Prokop, Gietema, Lammers, Vliegenthart, Oudkerk, Klaveren, Koning, Mali, de Jong.
Analysis and interpretation of data: Mets, Buckens, Zanen, Isgum, Ginneken, Prokop, Gietema, Lammers, Vliegenthart, Oudkerk, Klaveren, Koning, Mali, de Jong.
Drafting of the manuscript: Mets, Buckens, de Jong.
Critical revision of the manuscript for important intellectual content: Mets, Buckens, Zanen, Isgum, Ginneken, Prokop, Gietema, Lammers, Vliegenthart, Oudkerk, Klaveren, Koning, Mali, de Jong.
Statistical analysis: Buckens, Mets, de Jong.
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Study supervision: Prokop, Oudkerk, Klaveren, Koning, Mali, Lammers, de Jong.
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Online-Only Material: The eAppendix, 3 eTables, eEquation, and 3 eFigures are available at http://www.jama.com.
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We are, perhaps, uniquely among the earth's creatures, the worrying animal. We worry away our lives, fearing the future, discontent with the present, unable to take in the idea of dying, unable to sit still.

—Lewis Thomas (1913-1993)