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CHEST

Pulmonary function and CT biomarkers as risk factors for cardiovascular events in male lung cancer screening participants: the NELSON study

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Abstract

Objective The objective of this study was to investigate the association of spirometry and pulmonary CT biomarkers with cardiovascular events.

Methods In this lung cancer screening trial 3,080 male participants without a prior cardiovascular event were analysed. Fatal and non-fatal cardiovascular events were included. Spirometry included forced expiratory volume measured in units of one-second percent predicted (FEV_1%predicted) and FEV_1 divided by forced vital capacity (FVC; FEV_1/FVC). CT examinations were quantified for coronary artery calcium volume, pulmonary emphysema (perc15) and bronchial wall thickness (pi10). Data were analysed via a Cox proportional hazard analysis, net reclassification improvement (NRI) and C-indices.

Results 184 participants experienced a cardiovascular event during a median follow-up of 2.9 years. Age, pack-years and smoking status adjusted hazard ratios were 0.992 (95 % confidence interval (CI) 0.985-0.999) for FEV_1%predicted, 1.000 (95%CI 0.986-1.015) for FEV_1/FVC, 1.014 (95%CI 1.005-1.023) for perc15 per 10 HU, and 1.269 (95%CI 1.024-1.573) for pi10 per 1 mm. The incremental C-index (<0.015) and NRI (<2.8 %) were minimal. Coronary artery calcium volume had a hazard ratio of 1.046 (95%CI 1.034-1.058) per 100 mm^3, an increase in C-index of 0.076 and an NRI of 16.9 % (P<0.0001).

Conclusions Pulmonary CT biomarkers and spirometry measurements were significantly associated with cardiovascular events, but did not contain clinically relevant independent prognostic information for cardiovascular events.

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Key Points

- *Pulmonary CT biomarkers and spirometry are associated with cardiovascular events*
- *These pulmonary measurements do not contain clinically relevant independent prognostic information*
- *Only coronary calcium score improved cardiovascular risk prediction above age and smoking*

Keywords Cardiovascular diseases · Spirometry · Multi-detector computed tomography · Smoking · Mass screening

Abbreviations

COPD	Chronic obstructive pulmonary disease
CT	Computed Tomography
CVD	Cardiovascular disease
FEV1	Forced expiratory volume in one second (FEV1)
FEV_1%predicted	FEV_1 expressed as percent predicted
FVC	Forced vital capacity
ICD	International Classification of Diseases
Perc15	Density of the lungs quantified at the 15th percentile point
Pi10	Square root of wall area for a theoretical airway with 10-mm lumen perimeter
ROC	Receiver operating characteristic

Introduction

Lung cancer screening trials have mainly focused on the pulmonary consequences of smoking rather than cardiovascular events [1, 2]. Smoking is strongly associated with cardiovascular events [3]. Coronary calcifications, a strong predictor for cardiovascular events [4, 5], can be quantified using non-contrast Computed Tomography (CT) imaging with or without ECG-gating [6, 7]. Moreover, smoking is considered the most important modifiable risk factor for developing chronic obstructive pulmonary disease (COPD) [8–10]. COPD is thought to be an independent risk factor for cardiovascular events [11]. The pathologic features of COPD are destruction of lung parenchyma (emphysema) and inflammation of the small airways (bronchiolitis). CT can clearly visualize and quantify emphysema and bronchial wall thickness and this may reflect more distal small airway diseases [12–15].

Several studies observed an association between pulmonary function and cardiovascular events, even after correcting for confounders like smoking [16–20]. Forced expiratory volume in one second (FEV_1) is a robust accurate index reflecting pulmonary physiology and is associated with a higher risk of dying from cardiovascular conditions [17, 18]. Moreover, the annual rate of FEV_1 decline predicts cardiovascular mortality, independent of the initial predicted FEV_1 and cigarette smoking [21, 22]. On a sub-clinical level, a low FEV_1 is linked to an increased mean carotid artery intima-media thickness [23]. Despite these interesting associations it remains to be established whether these CT biomarkers or spirometry measurements do contain relevant predictive value for cardiovascular events.

The aim of our study, therefore, was to investigate the association of spirometry and pulmonary CT biomarkers with cardiovascular events and to determine the independent prognostic value of these measures for cardiovascular events.

Materials and methods

Ethics statement

This current study is an ancillary study of the Dutch and Belgian Lung Cancer Screening Trial (NELSON trial; ISRCTN63545820) approved by the Ministry of Health of The Netherlands and the institutional ethical boards of the participating centres. Written informed consent was obtained from all subjects.

Participants

A sample of Dutch and Belgian persons (50–75 years old) registered in population registries were inquired about their health and smoking behaviour [24]. Participants who had smoked ≥15 cigarettes per day for 25 years or ≥10 cigarettes for 30 years and were current smokers or had quit <10 years ago were included.

Pulmonary function testing

Spirometry was performed between 2004 and 2008 according to the American Thoracic Society and the European Respiratory Society guidelines using ZAN hardware (ZAN Messgeräte GmbH, Oberthulba, Germany) and Viasys hardware (Viasys Health Care, Yorba Linda, CA, USA) [25]. FEV_1 was expressed as percent predicted (FEV_1%predicted) and the FEV_1/FVC ratio was determined. A bronchodilator was not administered.

Computed tomography

Participants received a volumetric non-contrast enhanced chest CT at full inspiration. Non-ECG-gated images were obtained on 16-slice MDCT hardware with a 16 mm x 0.75 mm collimation (Sensation-16, Siemens Medical Solutions, Forchheim, Germany; Mx8000 IDT or Brilliance-16P CT, Philips Medical Systems, Best, the Netherlands). Imaging

acquisition was performed in a cranial-caudal direction. A 120-kV tube potential was applied in patients weighing less than 80 kg; in patients weighing more than 80 kg the tube potential was increased to 140 kV. The mAs settings were dependent on the CT hardware used and adjusted according to weight.

Pulmonary emphysema and bronchial wall thickness quantification

All pulmonary CT measures were automatically quantified with CIRRUS Lung 12.03 (Diagnostic Image Analysis Group, Nijmegen, The Netherlands; Fraunhofer MEVIS, Bremen, Germany). An observer with three years experience in chest CT checked the lung and airway segmentations for correctness. The lungs were extracted using an automatic segmentation algorithm [26]. The density of each voxel in the segmented lung volume was determined. The density of the lungs was quantified with the 15th percentile point (perc15). Perc15 is the threshold CT density value at which 15 % of the total voxels have a lower density. The perc15 was corrected for total lung capacity according to the following formula [27]:

$$\text{Adjusted percentile density} = \text{observed percentile density} \times (\text{total lung volume}/\text{predicted total lung capacity}).$$

Predicted total lung volume was calculated using the following formula [28]:

$$7.99 \times (\text{height in m}) - 7.08$$

Airway wall thickness was calculated for each subject by taking the square root of the wall area for a theoretical airway with a 10-mm lumen perimeter (Pi10). A detailed description of the quantitative analysis of bronchial dimensions used in this study was recently published elsewhere [29].

Coronary artery calcification quantification

A coronary calcium score was automatically obtained using dedicated, in-house developed software [30]. The algorithm applies a CT threshold of 130 HU in combination with three-dimensional connected-component labelling to identify potential calcifications. Calcifications were detected based on a probabilistic coronary calcium map, followed by a pattern recognition system detecting calcifications based on size, spatial and texture characteristics. Spatial features were established using a coronary calcium atlas providing an a priori probability for spatial appearance of coronary calcifications in a chest CT. Texture features were computed using Gaussian filters at multiple scales. All coronary calcifications were visually inspected and manually corrected if deemed necessary. Coronary calcium burden was expressed in total calcium volume (mm^3).

Outcome measures

Physician-diagnosed cause of death and hospital admission diagnosis was retrieved via probabilistic medical record linkage with the National Death Registry and the National Registry of Hospital Discharge Diagnoses [31]. We included fatal and non-fatal cardiovascular events that occurred between the CT examination and January 2008. Discharge diagnoses were classified using the 9th revision of the International Classification of Diseases (ICD) and causes of death were classified using the 10th revision of the ICD. Hypertensive disease (codes 401-405), ischemic heart disease (codes 410-414), heart failure (code 428), diseases of arteries, arterioles and capillaries (codes 440-448), cerebrovascular disease (codes 430-438) or other heart diseases (code 429) were included as cardiovascular events. Cardiovascular death predominated among the hospital admissions diagnoses. In cases with several valid hospital admissions the first hospital discharge diagnosis was applied. Participants with a cardiovascular history, defined as those with a cardiovascular event between 1995 and the CT, were excluded (n=448).

Statistical analysis

Normally distributed data are presented as mean ± standard deviation (SD) and compared with the unpaired Student's t test. Non-normally distributed data were summarized as the median plus the 25th-75th percentile and compared with the Mann-Whitney U test. Normal distribution was tested evaluating Quantile-Quantile plots. Imputation based on a regression model was applied to predict missing observations. The association between the occurrence of a cardiovascular event and potential predictors was analysed using multivariable Cox proportional hazard analysis adjusting for age, smoking status and pack-years (base risk model) in order to minimize bias based on those three factors. Adjusted hazard ratios with 95 % CIs were calculated. CT quantified emphysema, airway wall thickness, pulmonary function or coronary calcium volume were added separately. Coronary calcium volume was truncated at the 99th percentile (excluding 31 subjects) since biologically implausible values have a large impact on the prognostic accuracy. Bootstrap re-sampling (1,000 iterations) was applied to internally validate the predictors and adjust for over-optimism of the model. Net reclassification improvement (NRI) tables with cut points at 3 % and 6 % three-year risk were constructed to evaluate the added value of CT quantified emphysema, airway wall thickness, pulmonary function and coronary calcium volume in terms of reclassification [32]. ROCs were calculated for the different models. Kaplan–Meier survival curves for cardiovascular events were stratified by

Table 1 Baseline patient demographics and risk factors

	N=3080
Age (year), median (25th-75th)	59.2 (55.9-63.3)
Current smoker, n (%)	1765 (57.3)
Former smoker, n (%)	1315 (42.7)
Pack years (year), median (25th-75th)	38.0 (28.0-49.5)
FEV_1%predicted, (%) mean (±SD)	98.1 (18.5)
FEV_1/FVC (%), mean (±SD)	71.9 (9.5)
Emphysema Percentile15 (HU), mean (±SD)	−861.1 (145.1)
Bronchial wall thickness (Pi10) (mm), median (25th-75th)	2.4 (2.0-2.8)
Follow-up time (year), median (25th-75th)	2.9 (2.7-3.3)
Cardiovascular event, n (%)	184 (6.0)

quartiles of the individual predictor and a log-rank test for a linear trend was applied to test whether there was a linear trend between the quartiles. A *P*-value of 0.05 was considered statistically significant. All statistical analyses were performed using SPPS version 19 (SPSS Inc, Chicago, Illinois, USA) and R version 2.10.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Subject characteristics

The analysis included 3,080 male (median age: 59.2, 25th-75th percentile: 55.9-63.3) current (*n*=1765, 57.3 %) and former (*n*=1315, 42.7 %) smokers without prior cardiovascular disease (CVD) who underwent spirometry and CT lung cancer screening. Missing data were imputed for smoking status (*n*=6; 0.2 %), pack-years (*n*=10; 0.3 %), FEV_1%predicted (*n*=1; 0.0 %), FEV_1/FVC (*n*=1; 0.0 %), pi10 (*n*=180; 5.8 %) and perc15 (*n*=158; 5.1 %). The median follow-up period was 2.9 years (25th-75th percentile: 2.7-3.3) and 184 participants experienced a cardiovascular event. Cardiovascular event-free survival was 0.956 at one year, 0.948 at two years and 0.943 at three years. Detailed patient demographics are listed in Table 1.

Pulmonary function tests

The FEV_1%predicted (*P*=0.0018) was significantly lower in participants who experienced an event compared to those who did not. However, FEV_1/FVC (*P*=0.3918) was not significantly different (Table 2, Fig. 1a and b). In multivariate Cox proportional hazards models for cardiovascular events that controlled for age, smoking status and pack-years pulmonary function was a significant predictor, with a hazard ratio of 0.992 (95%CI 0.985-0.999) for FEV_1%predicted and 1.000 (95%CI 0.986-1.015) for FEV_1/FVC. Adding FEV_1%predicted or FEV_1/FVC to the base risk model did not yield an improved NRI at the 3-year follow-up; NRI was 1.0 % (*P*=0.72) for FEV_1%predicted and -0.6 % (*P*=0.56) for FEV_1/FVC (Table 3). Comparison of the C-indices confirmed this finding (Table 3).

CT emphysema and airway wall thickness

Measurements of emphysema and airway wall thickness were significantly worse (*P*=0.0249 and *P*=0.0074, respectively) in participants who experienced an event (Table 2). Kaplan-Meier plots in Fig. 1c and d show an association between quartiles of pulmonary CT measurements and a cardiovascular event. In multivariate Cox proportional hazards models for survival outcomes that controlled for age, smoking status and pack-years pulmonary CT measurements were significant predictors, with a hazard ratio of 1.014 (95%CI 1.005-1.023) for perc15 per 10 HU and 1.269 (95%CI 1.024-1.573) for pi10 per 1 mm. Nevertheless, adding perc15 or pi10 to the base risk model did not yield a significant improved risk reclassification at the 3-year follow-up: NRI 2.8 % (*P*=0.41) and -1.5 % (*P*=0.63), respectively. Also, the combination of perc15 and pi10

Table 2 Spirometry and CT biomarkers in lung cancer screening participants with and without incident cardiovascular events

Variable	No cardiovascular event		Incident cardiovascular event		*P* value
	Mean	95 %-CI	Mean	95 %-CI	
FEV_1%predicted (%)	98.3	97.7-99.0	94.0	91.1-96.8	0.0018
FEV_1/FVC (%)	71.9	71.5-72.2	71.3	69.7-72.8	0.3918
Perc15 (HU)	−862.6	−867.9- -857.3	−837.8	−856.9- -818.7	0.0249
Pi10* (mm)	2.4	2.0-2.8	2.5	2.1-2.9	0.0074
Coronary calcium volume (mm^3)*	122.9	6.2-505.6	588.5	139.4-1432.4	<0.0001

*Not normal distributed median+25th-75th percentile

Forced expiratory volume in one second predicted (FEV_1%predicted), FEV_1 divided by forced vital capacity (FEV_1/FVC), density of the lungs at the 15th percentile point (perc15), bronchial wall thickness (pi10), CI Confidence interval

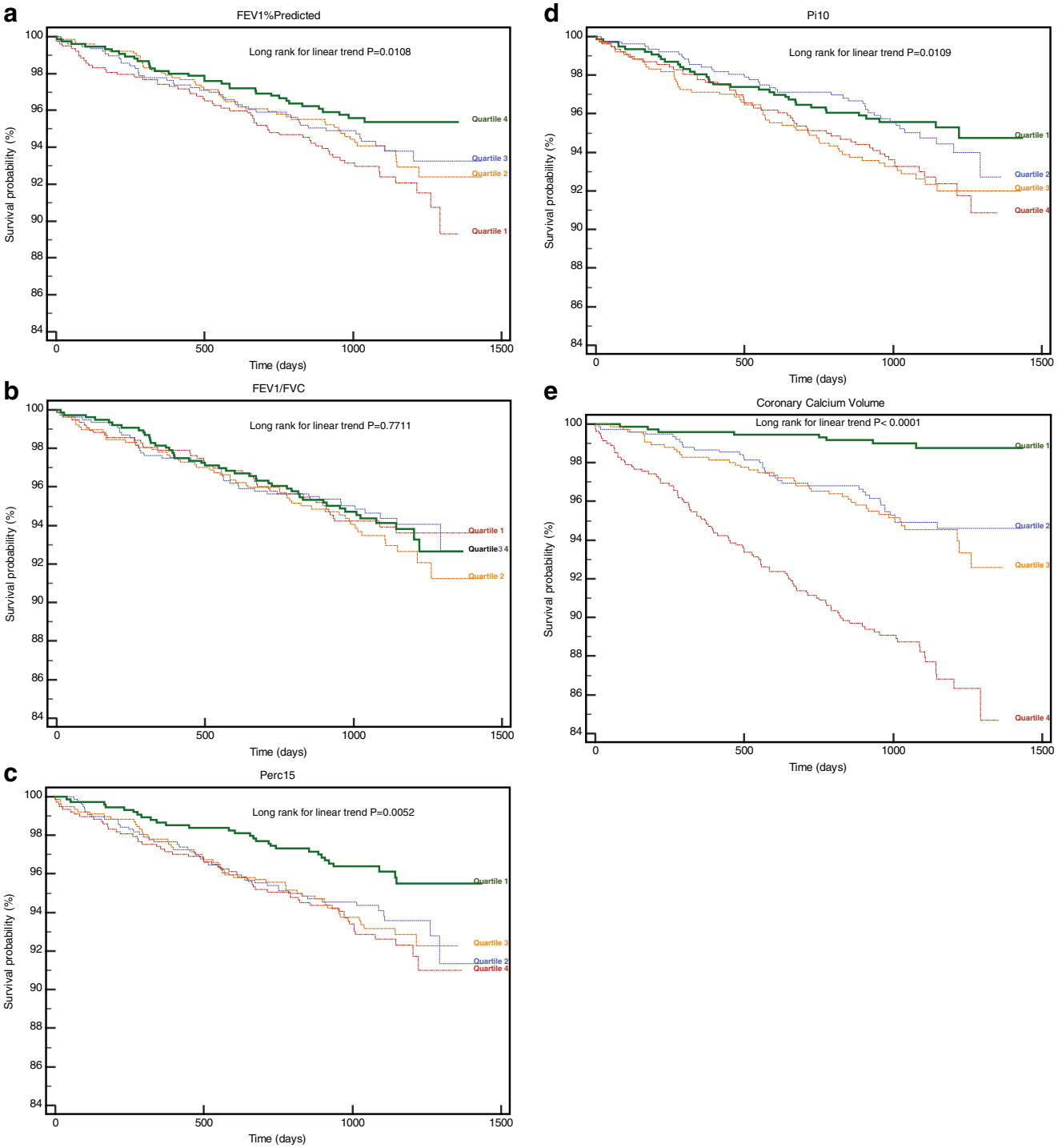

Fig. 1 Kaplan-Meier survival curves for incident cardiovascular events by quartile. (**a**) FEV_1%predicted; (**b**) FEV_1/FVC; (**c**) perc15; (**d**) pi10; and (**e**) coronary calcium volume. Tests for linear trend were performed across the quartiles

did not result in a significant improvement of NRI (Table 3). The C-index curves support these observations (Table 3).

CT coronary calcium score

Coronary calcium volume was significantly ($P<0.0001$) higher in participants who experienced an event (Table 2). Kaplan-Meier plots in Fig. 1e show a clear association between quartiles of coronary calcium volume and a cardiovascular event. In multivariate Cox proportional hazards models that controlled for age, smoking status and pack-years the coronary calcium volume was a significant predictor for cardiovascular events, with a hazard ratio of 1.046 (95%CI 1.034-1.058) per 100 mm^3. Moreover, adding the coronary

Table 3 Prognostic performance of CT biomarkers and spirometry for incident cardiovascular disease

Variable	C-statistic	P-value	NRI	P-value
Base model	0.623			
Base+FEV_1%predicted	0.631	0.3772	1.0	0.7206
Base+FEV_1/FVC	0.623	0.5706	−0.6	0.5632
Base+Perc15	0.634	0.2485	2.8	0.4111
Base+Pi10	0.626	0.6681	−1.5	0.6316
Base+Perc15+Pi10	0.638	0. 2234	1.4	0.7003
Base+Coronary calcium volume	0.699	<0.0001	16.9	<0.0001

Base model adjusted for age, smoking status and pack-years, forced expiratory volume in one second predicted (FEV_1%predicted), FEV_1 divided by forced vital capacity (FEV_1/FVC), density of the lungs at the 15th percentile point (perc15), bronchial wall thickness (pi10)

calcium volume to the Cox proportional hazard model containing age, pack-years and smoking status resulted in an NRI of 16.9 % ($P<0.0001$) and an improved C-index from 0.623 to 0.699 (Table 3).

Discussion

We found that pulmonary function as well as CT quantified emphysema and airway wall thickness in a male lung cancer screening population were associated with a modest but significant increase in cardiovascular event risk after adjustment for age, smoking status and pack-years. Nevertheless, neither pulmonary function nor CT measures of emphysema and bronchial wall thickness had sufficient independent prognostic value beyond age and smoking details. After adjustment for age, pack-years and smoking status only coronary calcium volume improved cardiovascular event prediction.

Several investigators have studied the association between pulmonary function and subsequent cardiovascular disease [16–18, 20]. Our data are consistent with these studies as we observed clear trends across quartiles of FEV_1%predicted, similar to Schroeder et al. [16], linking pulmonary function impairment with cardiovascular events. This association persisted after controlling for age, smoking status and pack-years. Sverzellati et al. investigated the association between CT quantified emphysema and the prediction of cardiovascular events [20]. Similar to our study, they found that coronary calcium was the strongest predictor for cardiovascular events, though in contrast we did observe an association between cardiovascular events and CT quantified emphysema and FEV1%. Also, data in a clinical population with visual scores showed that airway wall thickening is associated with future cardiovascular events [33]. Similar to CVD, COPD, emphysema and bronchiolitis are accompanied by low-grade systemic inflammation [8, 11, 34]. There is growing evidence indicating that cardiovascular disease is a major cause of death in COPD patients [35]. We confirmed that spirometry measures were associated with cardiovascular events after adjustment.

Besides confirming associations between pulmonary disease and cardiovascular events we quantified the independent value of these potential prognostic markers. Unfortunately, neither spirometry measurements nor pulmonary CT biomarkers improved cardiovascular event prediction. Coronary calcium volume, as a positive control, was the only risk factor that yielded a significant improved risk reclassification, which is consistent with previous research [5, 36]. Prior research showed that coronary calcium is superior to standard Framingham risk factors for prediction of cardiovascular events [37]. The current study confirms the prognostic value of coronary calcifications, even from non-gated chest CT in a lung cancer screening setting. The conclusion is that although smoking-induced pulmonary disease is clearly associated with cardiovascular events, spirometric or CT measurements did not improve CVD prognostication in our cohort.

An important strength of our study design is the large sample of lung cancer screening participants selected from the general population. Several limitations of this study should be mentioned. First, we included only males who were current smokers or had quit less than 10 years ago. Therefore, we cannot generalize our findings to women and non-smokers. Secondly, information of a history of CVD before the year 1995 was not obtainable because linkage of patient characteristics with hospital discharge registries was impossible before that date. This probably resulted in inclusion of some patients with a cardiovascular history in our analysis.

In conclusion, our study provides further insights into the relationship between CT-quantified emphysema and airway wall thickness and cardiovascular events in asymptomatic male lung cancer screening participants. Although spirometry and pulmonary CT measurements were significantly associated with cardiovascular events, they did not yield improved cardiovascular event risk stratification and are therefore not useful prognostic CVD biomarkers.

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obtained. Written informed consent was obtained from all subjects (patients) in this study.

Some study subjects or cohorts have been previously reported. This study is an ancillary study of a large lung cancer screening RCT (NELSON Study; ISRCTN63545820).

Methodology: prospective, prognostic study (original study was a randomised lung cancer screening trial), multi-center study.

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