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ORIGINAL ARTICLE

Vertebral bone attenuation in Hounsfield Units and prevalent vertebral fractures are associated with the short-term risk of vertebral fractures in current and ex-smokers with and without COPD: a 3-year chest CT follow-up study

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Abstract

Summary CT scans performed to evaluate chronic obstructive pulmonary disease (COPD) also enable evaluation of bone attenuation (BA; a measure of bone density) and vertebral fractures (VFs). In 1239 current/former smokers with ($n = 999$) and without ($n = 240$) COPD, the combination of BA and prevalent VFs was associated with the incident VF risk.

Introduction Chest CT scans are increasingly used to evaluate pulmonary diseases, including COPD. COPD patients have increased risk of osteoporosis and VFs. BA on CT scans is correlated with bone mineral density and prevalent VFs. The aim of this study was to evaluate the association between BA and prevalent VFs on chest CT scans, and the risk of incident VFs in current and former smokers with and without COPD.

Methods In participants of the ECLIPSE study with baseline and 1-year and 3-year follow-up CT scans, we evaluated BA in vertebrae T_4–T_{12} and prevalent and incident VFs.

Results A total of 1239 subjects were included (mean age 61.3 ± 8.0, 61.1% men, 999 (80.6%) COPD patients). The mean BA was 155.6 ± 47.5 Hounsfield Units (HU); 253 (20.5%) had a prevalent VF and 296 (23.9%) sustained an incident VF within 3 years. BA and prevalent VFs were associated with incident VFs within 1 (per − 1SD HR = 1.38 [1.08–1.76] and HR = 3.97 [2.65–5.93] resp.) and 3 years (per − 1SD HR = 1.25 [1.08–1.45] and HR = 3.10 [2.41–3.99] resp.), while age, sex, body mass index (BMI), smoking status and history, or presence of COPD was not. In subjects without prevalent VFs and BA, and for 1-year incidence, BMI values were associated with incident fractures (1 year, BA per − 1SD HR = 1.52 [1.05–2.19], BMI per SD HR = 1.54 [1.13–2.11]; 3 years, per − 1SD HR = 1.37 [1.12–1.68]).

Conclusions On CT scans performed for pulmonary evaluation in (former) smokers with and without COPD, the combination of BA and prevalent VFs was strongly associated with the short-term risk of incident VFs.

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Keywords COPD · Fracture risk assessment · Osteoporosis · Screening · Tobacco smoking

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease caused by significant exposure to noxious particles and gases, most often tobacco smoking, but also exposure to air pollution [1–4]. COPD is currently the fourth leading cause of deaths worldwide [5] and, although it is primarily a pulmonary disease, it also has significant extra-pulmonary comorbidities such as diabetes and gastrointestinal diseases [6, 7]. Another major comorbidity is osteoporosis, and reported prevalence of vertebral fractures (VFs) among COPD patients varied widely between 9 and 79% [8–17], depending on factors such as age, sex, ethnicity, medication, method of VF assessment, and vertebrae assessed.

In the evaluation of pulmonary diseases, chest computed tomography (CT) has emerged as a commonly used imaging modality, with more than 10 million chest CTs performed annually in the USA [18]. These scans could also contain prognostic valuable information about diseases such as atherosclerosis [19], bone density, and VFs.

Bone attenuation (BA) as measured on CT could serve as an alternative measurement to assess bone density; in a previous study, Romme et al. showed that BA measurements on chest CT correlated well with bone mineral density (BMD) measurements on dual-energy X-ray absorptiometry (DXA) in a COPD population ($r = 0.827$, $p < 0.001$) [20]. Opportunistic use of BA on CT scans for osteoporosis screening and for BMD estimation was reported in a review of 37 studies (using various measurement methods, measurement locations, and populations) [21]. They found variable correlations between BA and BMD by DXA ranging from 0.399 to 0.891 and suggested that studies about the predictive value of BA for fractures are needed. However, in postmenopausal women, it has been shown that prevalent VFs predict subsequent fractures independent of BMD [22, 23]. Smokers with and without COPD have been shown to have lower BA measured at the spine [24].

The relationship between BA and prevalent and incident VFs among smokers with and without COPD is largely unknown, while chest CT scans are commonly made for pulmonary evaluation in this patient group. Therefore, the aim of our study was to evaluate the association between BA and prevalent VFs measured on chest CT scans with the risk of incident VFs in current and former smokers with and without COPD.

Materials and methods

Subjects

We included subjects from the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; Clinicaltrials.gov identifier NCT00292552; GlaxoSmithKline study SCO104960). Detailed inclusion and exclusion criteria were described elsewhere [25–27]. In short, current or former smokers (40–75 years old) with moderate to very severe COPD (stages II–IV according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [28]: $FEV_1 < 80\%$ and $FEV_1/FVC < 0.7$ (FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity, both postbronchodilator and expressed as % predicted), see also online supplement), or without COPD ($FEV_1 > 85\%$, FEV1/FVC > 0.7), with a smoking history of at least 10 pack years, were included (1 pack year = 20 cigarettes per day for 1 year). Subjects with respiratory disease other than COPD were excluded, as well as subjects who were using oral glucocorticosteroids (GC) at baseline or who had an exacerbation requiring treatment in the 4 weeks prior to enrolment (for more exclusion criteria, see online supplement). Since we were interested in incidence of VFs as measured on CT, we only included subjects with complete availability of baseline, 1-year, and 3-year CT scans for this study.

Measurements

At baseline and 1-year and 3-year follow-ups, demographic and pulmonary information (FEV_1, FEV_1/FVC) were collected. Also, information about smoking behavior (pack years, current or former smoker) were evaluated. Chest CT scans (120-kV peak, 40 mAs, 1.00- or 1.25-mm volumetric acquisition, General Electric (GE) or Siemens; field of view to include both lungs) were performed without administration of contrast at full inspiration, at baseline and 1-year and 3-year follow-ups. CT scanners were used in daily clinical practice at all participating centers and calibrated regularly using industry and institutional standards.

Vertebral fracture assessment

Detailed information have been reported elsewhere [29]. Briefly, sagittal reformats containing the spine were adjusted in contrast to (partly) eliminate soft tissue. Subsequently, the sagittal reformats were superposed to create simulated lateral X-ray 2D images using Matlab (R2013a, MathWorks, Natick, MA, USA). VFs from T_1 to L_1 were semi-quantitatively evaluated and marked as "VF" or "no VF" on the 3-year image, after exclusion of deformities due to Scheuermann's disease, Schmorl's noduli, or platyspondyly. In case of a VF, vertebrae were morphometrically assessed using SpineAnalyzer software (Optasia Medical, Cheadle, UK [30–32]). If VFs were diagnosed, also the previous scan was quantitatively assessed (see also online supplement). VFs were classified according to

the grading method by Genant et al. (grade 1, 20–25% height reduction; grade 2, 25–40%; grade 3, > 40%) [33].

Incident VFs were defined as new VFs (from no VF to any grade of VF), or worsening of existing VFs (e.g., from grade 2 to grade 3) between baseline and 1 year, or between baseline and 3 years.

Bone attenuation

BA was measured on CT in regions of interest (ROIs) of approximately 275 mm^3 centered in vertebrae T_4 to T_{12}, using a self-written algorithm in Matlab (R2013a, MathWorks, Natick, MA, USA; ROI size slightly varying due to voxel size; see also Fig. 1). Fractured or deformed vertebrae were excluded from BA measurements. BA was measured as the mean of T_4 to T_{12} and expressed in Hounsfield Units (HU).

Main outcome measures

Main outcome measure was the incidence of VFs within 1 and within 3 years.

Possible determinants included in this study were age, sex, body mass index (BMI), smoking status, number of pack years, FEV_1, FEV_1/FVC, presence and severity of COPD, and BA at baseline. For the incidence of VFs, also prevalent VFs and change in BA within 1 or within 3 years were included.

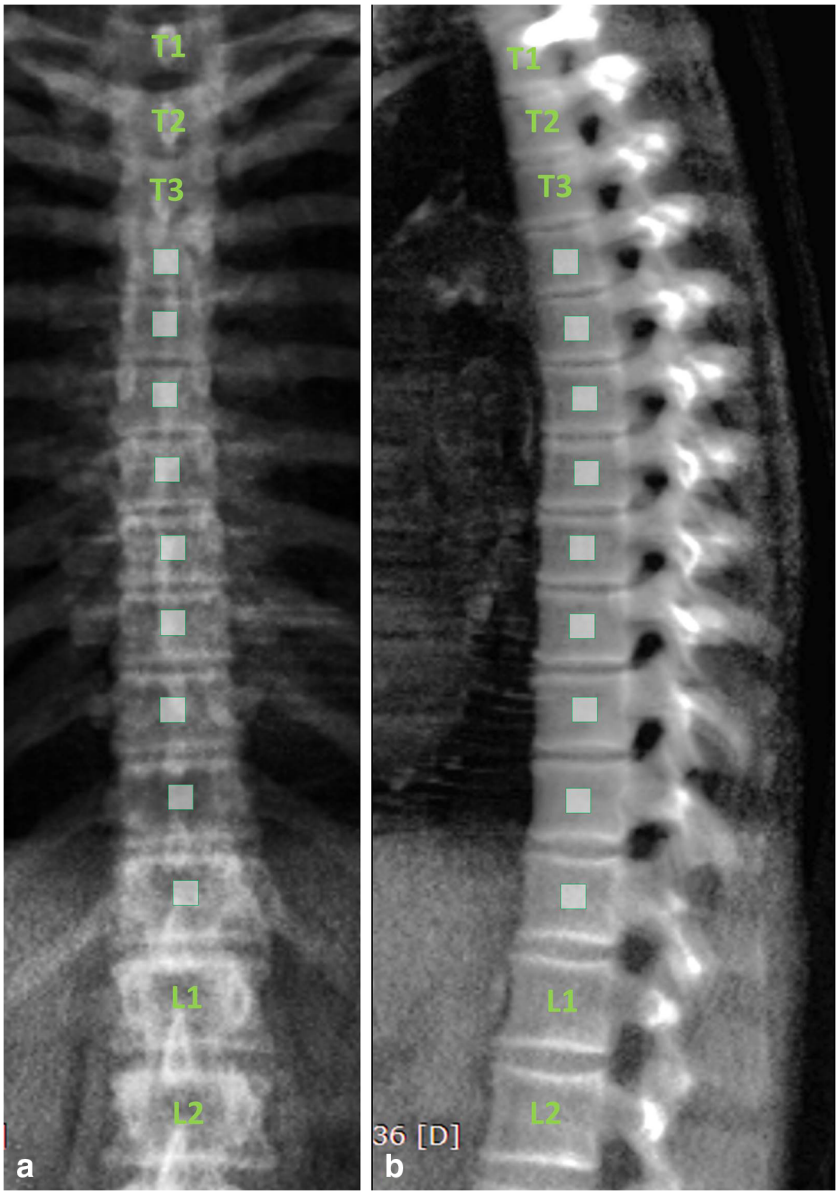

Fig. 1 Placement of ROIs in vertebrae T_4–T_{12}: the green-outlined semi-transparent cubes in the images represent the ROIs in vertebrae T_4–T_{12} in which BA was measured. Frontal (**a**) and sagittal (**b**) views of ROI placement

Statistics

Linear regression and correlation models were used to evaluate correlations between BA and the parameters age, sex, and BMI. BA and VF prevalence between subjects with or without COPD were compared using linear and logistic regression models respectively.

Logistic regression analysis (SAS 9.3, SAS Institute, Cary, NC, USA; LOGISTIC procedure) was used to assess univariate and multivariate relationships between possible determinants and prevalent VFs. Cox proportional hazard models (PHREG procedure) were used to assess univariate and multivariate relationships between determinants and incidence of VFs within 1 and 3 years. The latter was also applied to a subset of subjects without prevalent VFs.

Additionally, the population was divided into groups with low BA (0th–33.3th percentile), medium BA (33.3th–66.7th percentile), or high BA (66.7th–100th percentile) at baseline. Cox proportional hazard models were used to assess the effect of low or medium BA compared with high BA, and of prevalent VFs compared with no prevalent VFs on the incidence of VFs.

In all models, the level of statistical significance was set at $p < 0.05$.

Results

Out of a total of 2298 ECLIPSE subjects (327 subjects without and 1971 with COPD), 1478 subjects had the complete set of CT scans (baseline, 1-year and 3-year follow-ups). Of these, 239 subjects were excluded due to insufficient scan quality ($n = 156$), anatomy/lack of clear anatomic landmarks to identify vertebrae ($n = 14$), failure of the algorithm to edit the scan ($n = 60$), use of oral glucocorticosteroids (GC) at baseline ($n = 7$), or vertebral deformities of other nature than vertebral fractures throughout the spine (platyspondyly, $n = 1$; suspicion of Scheuermann's disease, $n = 1$).

Thus, 1239 subjects (240 (former) smokers without and 999 (former) smokers with COPD) were included (Table 1), of whom 253 (20.5%) were diagnosed with at least one prevalent VF.

BA was not significantly different between men (154.7 ± 46.8) and women (157.0 ± 48.6, $p = 0.3998$), but was correlated with age (r^2, −0.36, $p < 0.001$) and BMI (r^2, 0.19, $p < 0.001$). Between subjects with or without COPD, no significant difference was found in the mean baseline BA (151.3 ± 46.7 and 173.3 ± 46.6 resp., $p = 0.0699$) and in the percentage of subjects with one or more prevalent VFs (21.6 and 15.8 resp., $p = 0.8843$), with two or more prevalent VFs (10.3 and 4.2 resp., $p = 0.0578$), or with moderate or severe prevalent VFs (11.9 and 5.4% resp., $p = 0.1688$) after adjustment for age and sex (see also Table 1).

At 1-year and 3-year follow-ups, 120 (9.7%) and 296 (23.9%) subjects had at least one incident VF, respectively.

In a multivariate model, only male sex (odds ratio (OR) = 1.89 [95% CI 1.35–2.64]) and BA (per −1SD OR = 2.47 [2.01–3.03]) were significantly associated with prevalent VFs (Table 2).

In multivariate analyses, only baseline BA (per −1SD hazard ratio (HR) = 1.38 [1.08–1.76]) and prevalent VFs at baseline (HR = 3.97 [2.65–5.93]) were significantly associated with the risk of incident VFs within 1 year (Table 3). Only

Table 1 Clinical characteristics

		All subjects $n = 1239$		Subjects without COPD $n = 240$		Subjects with COPD $n = 999$	
Age (years, mean, SD)		61.3	8.0	55.0	8.7	62.8	7.0
Sex (M, *n*, %)		757	61.1	139	57.9	618	61.9
BMI (kg/m^2, mean, SD)		25.8	4.5	26.5	4.1	25.6	4.6
FFMI (kg/m^2, mean, SD)		17.6	3.2	18.7	2.7	17.4	3.2
Smoking status	Current smoker (*n*, %)	524	20.5	153	63.8	371	37.1
	Former smoker (*n*, %)	715	79.5	87	36.3	628	62.9
Pack years (mean, SD)		43.3	24.8	31.6	20.2	46.1	25.0
Post-dose FEV_1 (L, mean, SD)		1.8	1.0	3.4	0.7	1.4	0.5
Post-dose FEV_1 (%pred, mean, SD)		61.1	28.0	109.4	11.8	49.6	15.7
Post-dose FVC (L, mean, SD)		3.4	1.0	4.3	1.0	3.1	0.9
Post-dose FVC (%pred, mean, SD)		94.4	20.7	113.9	13.4	89.7	19.4
Post-dose FEV_1/FVC (%pred, mean, SD)		66.7	21.7	101.4	6.6	58.5	14.7
Bone attenuation (HU, mean, SD)		155.6	47.5	173.3	46.6	151.3	46.7
≥ 1 prevalent VF (*n*, %)		253	20.5	38	15.8	215	21.5
≥ 2 prevalent VF (*n*, %)		113	9.1	10	4.2	103	10.3
Grade 2/3 VF (*n*, %)		132	10.7	13	5.4	119	11.9
Incident VF within 1 year (*n*, %)		120	9.7	17	7.1	103	10.3
Incident VF within 3 years (*n*, %)		296	23.9	48	20.0	248	24.8

COPD, chronic obstructive pulmonary disease; *BMI*, body mass index; *FFMI*, fat-free mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *HU*, Hounsfield Units; *VF*, vertebral fracture

FEV_1 and FEV_1/FVC are both post-bronchodilator

Table 2 Determinants of prevalent vertebral fractures

	Without prevalent VFs $n = 984$		With prevalent VFs $n = 253$		Univariate		Multivariate	
					OR	95% CL	OR	95% CL
Age (years, mean, SD) (OR per SD)	60.6	8.0	64.0	7.2	1.599	[1.371–1.866]	1.170	[0.964–1.420]
Sex (M, *n*, %) (OR vs. F)	570	57.9	185	73.1	1.976	[1.456–2.682]	1.887	[1.350–2.639]
BMI (kg/m^2, mean, SD) (OR per SD)	25.8	4.5	25.7	4.6	0.979	[0.840–1.140]	1.160	[0.968–1.390]
Current smoker (*n*, %) (OR vs former)	434	44.1	89	35.2	0.688	[0.516–0.916]	0.874	[0.626–1.219]
Pack years (mean, SD) (OR per SD)	42.3	23.6	47.2	28.7	1.199	[1.054–1.365]	1.091	[0.938–1.268]
FEV_1 (%pred, mean, SD) (OR per SD)	62.2	28.4	57.2	26.2	0.829	[0.716–0.960]	1.081	[0.725–1.612]
FEV_1/FVC (%pred, mean, SD) (OR per SD)	67.6	21.8	63.4	21.1	0.817	[0.706–0.946]	0.825	[0.582–1.172]
COPD (yes, *n*, %) (OR vs. no COPD)	782	79.5	215	85.0	1.461	[1.001–2.132]	0.663	[0.311–1.411]
GOLD II (yes, *n*, %) (OR vs. no COPD)	367	37.3	99	39.1	1.434	[0.950–2.163]		
GOLD III (yes, *n*, %) (OR vs. no COPD)	333	33.8	87	34.4	1.388	[0.913–2.112]		
GOLD IV (yes, *n*, %) (OR vs. no COPD)	82	8.3	29	11.5	1.880	[1.088–3.249]		
BA (HU, mean, SD) (OR per SD)	162.6	46.2	128.2	42.6	2.488	[2.076–2.983]	2.468	[2.009–3.033]

Missing: 2 subjects (with COPD GOLD II)

VF, vertebral fracture; *CL*, confidence limits; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *COPD*, chronic obstructive pulmonary disease; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease; *HU*, Hounsfield Units

FEV_1 and FEV_1/FVC are both post-bronchodilator

ORs per SD: age SD = 8; BMI SD = 5; pack years SD = 25; FEV_1 (%predicted) SD = 28; FEV_1/FVC (%predicted) SD = 22; BA SD = − 47

baseline BA (per − 1SD HR = 1.25 [1.08–1.45]) and prevalent VFs (HR = 3.10 [2.41–3.99]) were significantly associated with incidence of VFs within 3 years.

When combining information on BA and prevalent VFs, the 1-year-adjusted HR for subjects with prevalent VFs in the lowest BA tertile was 7.5 [95% CI 4.1–14.0], and the 3-year-adjusted HR was 5.4 [3.7–8.1], compared with subjects without prevalent VFs in the highest BA tertile (Fig. 2).

In subjects without prevalent VFs ($n = 984$), BMI (per + 1SD HR = 1.54 [1.13–2.11]) and baseline BA (per − 1SD HR = 1.52 [95% CI 1.05–2.19]) were significantly associated with the risk of incident VFs within the first year (Table 4). Baseline BA was the only significant determinant for the risk of incident VFs within 3 years (per − 1SD HR = 1.37 [1.12–1.68]).

Discussion

In current and former heavy smokers with or without COPD, we found that baseline BA at the thoracic spine was associated with prevalent VFs and with the short-term risk of incident VFs at 1 and 3 years. However, the presence of one or more prevalent VFs was a much stronger determinant for the short-term VF risk than baseline BA. The combination of assessment of both BA and the presence of VFs provided clinical relevant information about the short-term VF risk in the studied population. In contrast, age, sex, BMI, having COPD, smoking status, and smoking history were not significantly contributing to the risk of VFs when prevalent VFs and baseline BA were included in the analyses.

Although BA measurements as presented in this study are not ready for application to individual cases in its current form, we have provided additional evidence that there is potential in opportunistic screening for osteoporosis and fracture risk using direct BA measurements from chest CT scans. This is in line with a recent review by Gausden et al. who reported that future research efforts should focus on identifying specific anatomic regions in high-risk patients using diagnostic CT [21]. More specifically, we have shown this in a population of smokers and COPD patients who are at an increased fracture risk, and for which diagnostic pulmonary CT scans are regularly made.

The presence of prevalent VFs was a strong determinant for incident VFs, which is in line with findings previously reported in postmenopausal women [34]. Even though BA was significantly associated with incident VFs, a prevalent VF was a stronger determinant, as illustrated in Fig. 2. The independent additive value of BA and prevalent VFs on incident VF risk is in line with that of previous studies [23, 35].

Only few studies reported an association between CT-based bone density measurements in the spine and incident fractures. In line with our findings, Baum et al. reported a difference in the lumbar spine density (L_1–L_3) between subjects with and without VFs (prevalent as well as incident), using converted BMD values requiring a reference phantom [36]. Also, Lee et al. reported lower BA (measured in vertebra L_1) in subjects with incident fragility fractures, including vertebral fractures [35].

Table 3 Determinants of incident vertebral fractures within 1 and 3 years

	Without incident VFs		With incident VFs		Univariate		Multivariate (with COPD as total)	
1 year	$n = 1114$		$n = 120$		HR	95% CL	HR	95% CL
Age (years, mean, SD) (HR per SD)	61.0	8.0	63.8	7.2	1.41	[1.157–1.712]	1.13	[0.886–1.443]
Sex (M, *n*, %)	663	59.5	89	74.2	1.84	[1.223–2.769]	1.48	[0.960–2.290]
BMI (kg/m^2, mean, SD) (HR per SD)	25.8	4.6	25.1	4.3	0.85	[0.693–1.039]	0.97	[0.771–1.210]
Current smoker (*n*, %) (HR vs. former)	478	42.9	45	37.5	0.82	[0.564–1.180]	1.01	[0.678–1.514]
Pack years (mean, SD) (HR per SD)	43.1	24.8	44.7	24.8	1.06	[0.891–1.255]	0.93	[0.770–1.129]
FEV_1 (%pred, mean, SD) (HR per SD)	61.8	28.0	55.1	27.3	0.79	[0.645–0.962]	0.77	[0.466–1.277]
FEV_1/FVC (%pred, mean, SD) (HR per SD)	67.2	21.7	62.2	21.7	0.80	[0.659–0.972]	1.01	[0.654–1.573]
COPD (yes, *n*, %) (HR vs. no COPD)	891	80.0	103	85.8	1.46	[0.875–2.442]	0.57	[0.216–1.481]
GOLD II (yes, *n*, %) (HR vs. no COPD)	422	37.9	42	35.0	1.28	[0.727–2.245]		
GOLD III (yes, *n*, %) (HR vs. no COPD)	377	33.8	42	35.0	1.42	[0.806–2.486]		
GOLD IV (yes, *n*, %) (HR vs. no COPD)	92	8.3	19	15.8	2.42	[1.256–4.649]		
BA (HU, mean, SD) (HR per − SD)	158.6	46.7	127.9	46.4	1.99	[1.613–2.454]	1.38	[1.081–1.759]
ΔBA 1Y (HU, mean, SD) (HR per SD)	− 2.4	9.6	− 1.3	16.2	1.08	[0.930–1.262]	1.01	[0.852–1.186]
≥ 1 prevalent VF (*n*, %) (HR vs. no VF)	179	16.1	71	59.2	5.70	[3.963–8.207]	3.97	[2.654–5.934]
≥ 2 prevalent VF (*n*, %) (HR vs. no or 1 VF)	68	6.1	43	35.8	5.65	[3.890–8.205]		
VF grade 2/3 (*n*, %) (HR vs. no or gr1 VF)	89	8.0	42	35.0	4.53	[3.116–6.598]		
3 years	$n = 941$		$n = 296$		HR	95% CL	HR	95% CL
Age (years, mean, SD) (HR per SD)	60.7	8.0	63.2	7.5	1.29	[1.145–1.460]	1.09	[0.936–1.267]
Sex (M, *n*, %)	548	58.2	207	69.9	1.48	[1.158–1.903]	1.22	[0.935–1.584]
BMI (kg/m^2, mean, SD) (HR per SD)	25.8	4.5	25.5	4.6	0.93	[0.817–1.054]	1.01	[0.877–1.162]
Current smoker (*n*, %) (HR vs. former)	403	42.8	120	40.5	0.93	[0.738–1.174]	1.10	[0.857–1.424]
Pack years (mean, SD) (HR per SD)	42.5	23.9	45.8	27.4	1.10	[0.989–1.220]	1.01	[0.904–1.137]
FEV1 (%pred, mean, SD) (HR per SD)	62.2	28.2	57.9	27.2	0.89	[0.785–0.999]	0.93	[0.678–1.266]
FEV1/FVC (%pred, mean, SD) (HR per SD)	67.5	21.7	64.2	21.5	0.89	[0.785–0.998]	0.97	[0.734–1.275]
COPD (yes, *n*, %) (HR vs. no COPD)	749	79.6	248	83.8	1.24	[0.913–1.694]	0.74	[0.409–1.323]
GOLD II (yes, *n*, %) (HR vs. no COPD)	358	38.0	109	36.8	1.17	[0.831–1.639]		
GOLD III (yes, *n*, %) (HR vs. no COPD)	313	33.3	106	35.8	1.26	[0.899–1.779]		
GOLD IV (yes, *n*, %) (HR vs. no COPD)	78	8.3	33	11.1	1.49	[0.954–2.316]		
BA (HU, mean, SD) (HR per − SD)	161.8	45.9	136.0	47.3	1.59	[1.400–1.806]	1.25	[1.076–1.448]
ΔBA 3Y (HU, mean, SD) (HR per SD)	− 8.7	14.1	− 8.1	14.3	1.03	[0.922–1.158]	0.99	[0.876–1.113]
≥ 1 prevalent VF (*n*, %) (HR vs. no VF)	105	11.2	147	49.7	3.88	[3.087–4.873]	3.10	[2.410–3.985]
≥ 2 prevalent VF (*n*, %) (HR vs. no or 1 VF)	35	3.7	77	26.0	3.54	[2.734–4.596]		
VF grade 2/3 (*n*, %) (HR vs. no or gr1 VF)	49	5.2	83	28.0	3.26	[2.533–4.206]		

Missing 1 year: 5 subjects (5 males; 4 GOLD 2, 1 GOLD 3); missing 3 year: 2 subjects (2 males; 1 GOLD II, 1 GOLD III)

VF, vertebral fracture; *CL*, confidence limits; *COPD*, chronic obstructive pulmonary disease; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease; *BA*, bone attenuation; *HU*, Hounsfield Units

FEV_1 and FEV_1/FVC are both post-bronchodilator; HR for BA given per negative value to compare subjects with lower BA to subjects with higher BA; negative ΔBA means a decrease in BA, HR per SD in larger decrease

HR's per SD: age SD = 8; BMI SD = 5; pack years SD = 25; FEV_1 (%predicted) SD = 28; FEV_1/FVC (%predicted) SD = 22; BA SD = 47; ΔBA 1 year SD = 10 HU; ΔBA 3 year SD = 14 HU

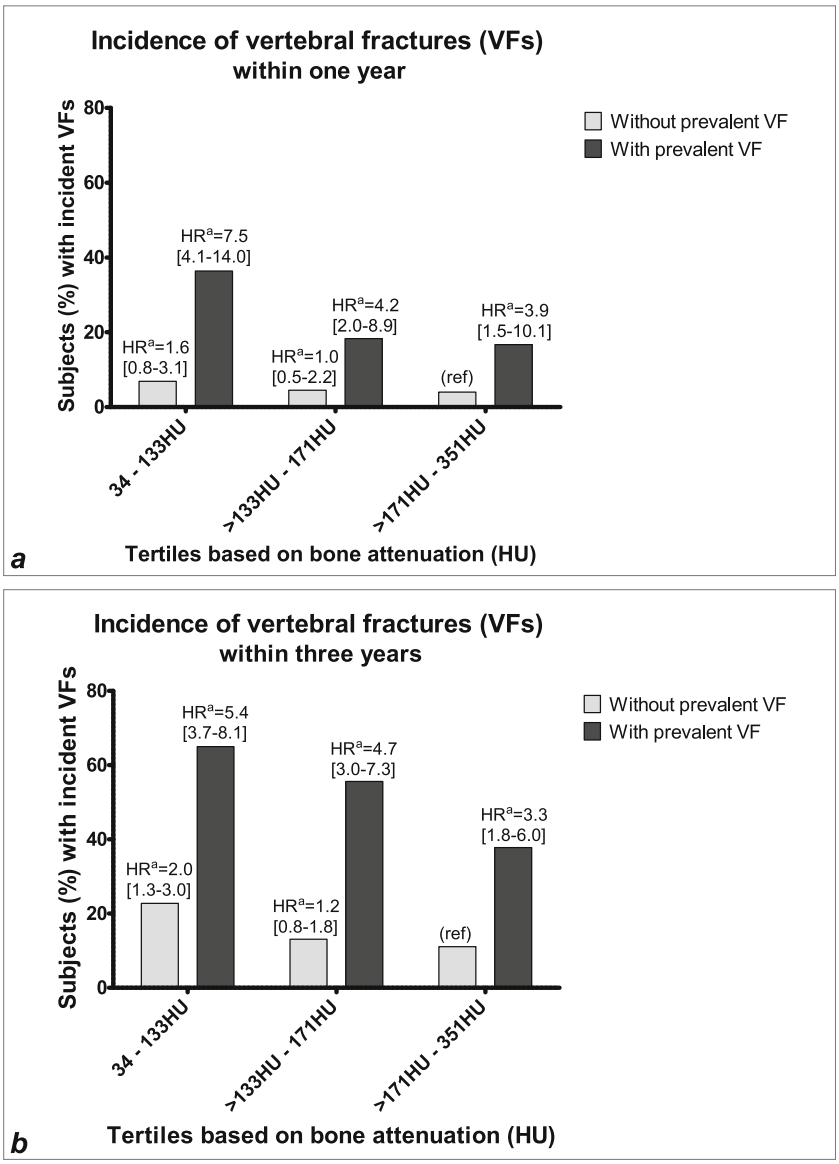

Fig. 2 Incidence of vertebral fractures (VFs) within 1 year (**a**) and within 3 years (**b**), stratified by bone attenuation tertiles (measured in Hounsfield Units (HU)) and prevalence of VFs at baseline. HR[a] adjusted for age, sex, body mass index, having COPD, pack years, and smoking status. Reference group is highest bone attenuation tertile, without prevalent VFs at baseline

Wang et al. measured bone density in the lumbar spine (L_1) using quantitative CT (QCT) and found a HR of 9.4 [4.1–21.6] (clinically presented VF risk) [37]. Although the HRs presented in our results are lower than the HRs presented by Wang et al., our results were comparable to results published by Samelson et al., who reported the association between volumetric BMD in the distal radius and tibia using HR-pQCT (high-resolution peripheral quantitative computed tomography) and risk of clinical fracture in men and women with HRs ranging from 1.32 [1.21–1.44] to 1.51 [1.38–1.65] (adjusted for cohort and FRAX) [38].

In subjects without prevalent VFs, a lower baseline BA and a higher BMI were associated with the risk of VFs within 1 year (Table 4), while only baseline BA was associated with the 3-year VF risk. The association between BMI and fracture risk is still unclear [39]. In smokers with and without COPD, Jaramillo et al. reported that, although BMI was associated with higher bone density, BMI was associated with a higher risk of vertebral fracture [17]. One reason may be biomechanics since applied loads due to for example lifting or holding something are higher in obese subjects, as has been shown in women [40].

We found no significant difference in BA between subjects with or without COPD after adjustment for age and sex, which is in contrast with the study of De Jong et al. [8]. However, that study population was slightly different from our study (males only, fewer pack years, fewer prevalent VFs, and fewer subjects with COPD). In addition, BA was measured only in vertebra L_1. When we performed an analysis of only men and used BA measured in T_{12}, we also found a significant difference between subjects with or without COPD ($p = 0.0359$). Our findings are in line with the results published by Romme et al. [24], who applied

Table 4 Determinants of incident VFs within 1 and 3 years in subjects without prevalent VFs

	Without incident VFs		With incident VFs		Univariate		Multivariate (with COPD as total)	
1 year	*n* = 935		*n* = 49		HR	95% CL	HR	95% CL
Age (years, mean, SD) (HR per SD)	60.5	8.1	62.3	7.7	1.25	[0.934–1.674]	1.11	[0.774–1.584]
Sex (M, *n*, %)	537	57.4	33	67.3	1.50	[0.825–2.721]	1.35	[0.728–2.518]
BMI (kg/m^2, mean, SD) (HR per SD)	25.7	4.5	27.0	4.2	1.33	[1.000–1.780][a]	1.54	[1.126-2.107]
Current smoker (*n*, %) (HR vs. former)	415	44.4	19	38.8	0.80	[0.452–1.426]	1.13	[0.600–2.140]
Pack years (mean, SD) (HR per SD)	42.3	23.6	43.5	25.3	1.05	[0.791–1.396]	0.94	[0.686–1.289]
FEV_1 (%pred, mean, SD) (HR per SD)	62.5	28.3	56.5	29.1	0.81	[0.594–1.091]	0.77	[0.355–1.664]
FEV_1/FVC (%pred, mean, SD) (HR per SD)	67.8	21.7	62.8	21.9	0.79	[0.585–1.069]	0.64	[0.328–1.265]
COPD (yes, *n*, %) (HR vs. no COPD)	742	79.4	40	81.6	1.15	[0.557–2.366]	0.24	[0.052–1.074]
GOLD II (yes, *n*, %) (HR vs. no COPD)	353	37.8	14	28.6	0.86	[0.371–1.978]		
GOLD III (yes, *n*, %) (HR vs. no COPD)	314	33.6	19	38.8	1.28	[0.579–2.830]		
GOLD IV (yes, *n*, %) (HR vs. no COPD)	75	8.0	7	14.3	1.92	[0.714–5.145]		
BA (HU, mean, SD) (HR per − SD)	163.4	46.0	147.5	47.7	1.46	[1.058–2.016]	1.52	[1.051–2.188]
ΔBA 1Y (HU, mean, SD) (HR per SD)	− 2.6	9.6	− 1.4	10.6	1.12	[0.846–1.482]	1.03	[0.760–1.403]
3 years	*n* = 836		*n* = 148		HR	95% CL	HR	95% CL
Age (years, mean, SD) (HR per SD)	60.4	8.1	61.8	7.7	1.17	[0.994–1.384]	1.05	[0.858–1.286]
Sex (M, *n*, %)	472	56.5	98	66.2	1.42	[1.013–2.001]	1.38	[0.967–1.967]
BMI (kg/m^2, mean, SD) (HR per SD)	25.7	4.5	26.2	4.8	1.10	[0.920–1.305]	1.17	[0.962–1.415]
Current smoker (*n*, %) (HR vs. former)	370	44.3	64	43.2	0.97	[0.698–1.337]	1.10	[0.768–1.579]
Pack years (mean, SD) (HR per SD)	41.8	23.2	45.3	26.0	1.13	[0.969–1.315]	1.07	[0.908–1.262]
FEV_1 (%pred, mean, SD) (HR per SD)	62.4	28.4	60.8	28.4	0.95	[0.811–1.122]	1.04	[0.677–1.611]
FEV_1/FVC (%pred, mean, SD) (HR per SD)	67.8	21.8	66.5	21.7	0.95	[0.806–1.121]	0.88	[0.596–1.285]
COPD (yes, *n*, %) (HR vs. no COPD)	663	79.3	119	80.4	1.06	[0.706–1.591]	0.75	[0.334–1.680]
GOLD II (yes, *n*, %)	316	37.8	51	34.5	0.97	[0.614–1.527]		
GOLD III (yes, *n*, %)	278	33.3	55	37.2	1.15	[0.734–1.804]		
GOLD IV (yes, *n*, %)	69	8.3	13	8.8	1.10	[0.574–2.124]		
BA (HU, mean, SD) (HR per − SD)	164.8	45.5	150.5	48.3	1.34	[1.122–1.611]	1.37	[1.118–1.677]
ΔBA 3Y (HU, mean, SD) (HR per SD)	− 8.7	14.2	− 8.0	13.0	1.05	[0.889–1.230]	0.97	[0.821–1.153]

VF, vertebral fracture; *CL*, confidence limits; *COPD*, chronic obstructive pulmonary disease; *BMI*, body mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease; *HU*, Hounsfield Units

[a] [1.000223–1.780165]

FEV_1 and FEV_1/FVC are both post-bronchodilator; HR for BA given per negative value to compare subjects with lower BA to subjects with higher BA; negative ΔBA means a decrease in BA, HR per SD in larger decrease

HR's per SD: age SD = 8; BMI SD = 5; pack years SD = 25; FEV_1 (%predicted) SD = 28; FEV_1/FVC (%predicted) SD = 22; BA SD = 47; ΔBA 1 year SD = 10 HU; ΔBA 3 year SD = 14 HU

a different BA measurement in largely the same population as the current manuscript. They reported a significant difference in BA between COPD patients and never smokers, underlining that smoking is an important risk factor, which is well known from literature [41–43].

BA was not significantly different between subjects with or without COPD or between men and women, but was correlated with age and BMI. It may seem unexpected that we did not find a significant difference in BA between men and women (154.7 ± 46.8 and 157.0 ± 48.6 resp., $p = 0.3998$). However, it should be noted that this is a specific population, in which men had higher odds of a prevalent VF (Table 2).

The presence of COPD or disease severity by means of GOLD stage significantly increased neither the odds for prevalent VFs in multivariate models nor the risk of incident VFs in our study. This contrasts with Nuti et al., who reported a significant relationship between COPD severity and prevalence of VFs, more so in men than in women (in that COPD population, 13.3% of men and 55.1% of women were never smokers) [14].

In accordance with the literature [8, 44–46], we found a significant association between BA measured in the spine and VFs. The reported baseline BA values (total population, 155.5 HU; without prevalent VFs, 162.2 HU; with prevalent VFs, 128.3 HU) were in the same range as the values reported by Kim et al. [45] and Meredith et al. [46]. Lower BA values have been reported by Graffy et al. [44] and De Jong et al. [8]. All studies used slightly different CT protocols and BA measurement methods.

This study has several limitations. First, there could be some limitations arising from the selection of subjects by ECLIPSE, and selection of subjects from ECLIPSE for this study, limiting the applicability to the general population of smokers with or without COPD. ECLIPSE recruited subjects from outpatient clinics (COPD patients) or through site databases and advertisement in local newspapers, etc. (subjects without COPD). Subjects with COPD GOLD stage I, subjects using oral GC at baseline, or subjects of ethnic origin other than non-Hispanic whites were excluded, and only a limited number of subjects with COPD GOLD stage IV were included. Subsequently, we only included subjects with a full set of three CT scans, i.e., subjects willing to and able to complete the study (see also e-Table 1 in the online supplement).

Second, we have included "smoking status" as a confounder, but this parameter was only evaluated at baseline and not re-evaluated during the study.

Third, due to the nature of the scans, VFs were only assessed in T_1–L_1. The lack of assessment of vertebrae L_2–L_5 may have underestimated the prevalence and incidence of VFs, and may limit the generalizability of the presented results to comparable populations. In addition, several studies have presented the results of BA measurements in the lumbar vertebrae; since such results were not available in our data, comparing results is difficult.

Fourth, we had no data available about menopausal status in the female subjects.

Lastly, there are some limitations concerning the evaluation of BA to discuss. The ROI size was approximately 275 mm^3 in all vertebrae, thereby ignoring the difference in the structure within the vertebral body which possibly results in over- or underestimation of BA in substantially smaller or larger vertebrae. In addition, ROIs were placed semi-automatically without avoiding inhomogeneous areas which is done in manual measurements. However, the 3D BA in T_4–T_{12} measured by our method was highly correlated with manually selected 2D measurements in T_4, T_7, and T_{10} ($r^2 = 0.89$, data not published).

Different types of scanners were used for the ECLIPSE study (both GE and Siemens). We have not tested the possible effect of different scanner manufacturers and types on the BA measurement, but CT scanners were used in daily clinical practice at all participating centers and calibrated regularly using industry and institutional standards. However, the lack of cross-calibration between scanners might weaken the predictive value of baseline BA for the incidence of VFs. Engelke et al. state in the "2015 International Society for Clinical Densitometry (ISCD) Official Positions" that direct BA measurements in HU can differentiate between low and high bone density at a certain difference (for example, a difference in BMD of 50 mg/cm^3), but that stability of the scanners is very important [47]. Unfortunately, CT scanners were not cross-calibrated and data about the stability of the scanners used in the ECLIPSE study are lacking.

The method was semi-automatic and therefore depends on user-input. In a substudy of 25 subjects, ICC (intraclass correlation coefficient) of triple BA measurements on the same CT scan showed excellent agreement (ICC = 0.998 [0.996–0.999]; single measures, two-way random, absolute agreement, data not published).

There were no rescan data available. Since BA is not expected to decrease drastically within 1 year, we have used the BA measurements of baseline and 1 year of a random subset of 25 subjects, to simulate rescan data. In this subset, the ICC was 0.986 (0.970–0.994). The short-term precision error according to Glüer et al. [48] is 3.3 (expressed in percentage, 2.1%) when the baseline and 1-year results were compared.

Our study has several strengths. The ECLIPSE study is a large, multicenter study that included both males and females, increasing the generalizability of the results if the limitations mentioned above are kept in mind. This is, to our knowledge, the only large study including COPD patients with a CT scan at three different time points, which enables the research of incident VFs and the possible relationship with BA in this population. BA was measured semi-automatically in 3D ROIs at multiple vertebral levels in the thoracic spine. Because it is semi-automatic, it is relatively quick and easy and eliminates (part of) the human interpretation when choosing the ROI to assess BA.

Conclusions

In (former) heavy smokers with or without COPD, BA and prevalent VFs evaluated on chest CT scans performed in the context of evaluating pulmonary diseases are associated with the short-term risk of incident VFs. This indicates that assessment of BA and especially the presence of a prevalent VF on clinical chest CT scans are important to identify smokers at high risk of VFs.

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Compliance with ethical standards

Conflicts of interest Mayke J. van Dort has nothing to disclose. Piet Geusens reports grants, speaker fees, and advisory board from Amgen, grants from Pfizer, grants from MSD, grants from UCB, grants from Abbott, grants and speaker fees from Lilly, grants from BMS, grants from Novartis, grants from Roche, and grants from Will Pharma, outside the submitted work. Johanna H.M. Driessen has nothing to disclose. Elisabeth A.P.M. Romme has nothing to disclose. Frank W.J.M. Smeenk has nothing to disclose. Emiel F.M. Wouters reports board membership at Boehringer, grants and speaker fees from AstraZeneca, grants and speaker fees from GSK, speaker fees from Novartis, and speaker fees from Chiesi, outside the submitted work. Joop P.W. van den Bergh reports grants from Eli Lilly, grants from Will Pharma, and grants from Amgen, outside the submitted work.

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