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Chapter 1

General introduction

Non-communicable diseases (NCDs)

Non-communicable diseases (NCDs) accounted for 41 million deaths worldwide in 2016, which equals 71% of all deaths.[1] Four major groups of NCDs can be defined: cardiovascular diseases such as ischaemic heart disease or stroke (17.9 million deaths in 2016), cancer (9.0 million), respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma (3.9 million), and diabetes (1.6 million).[1] According to the 2008 WHO's world health statistics, COPD was the fourth-leading cause of death worldwide in 2004 (5.1% of all deaths) and is expected to be the third-leading cause by 2030 (8.6% of all deaths),[2] while the Global Burden of Disease study 2010 concluded that COPD already has become the third-leading cause.[3] These numbers indicate that COPD is one of the larger NCDs. For comparison: ischaemic heart disease retains at the top of the WHO list (12.2% and 14.2% of all deaths in 2004 and 2030 respectively) followed by cerebrovascular disease (9.7% and 12.1% resp.).[2]

In a systematic review, it was estimated that there were approximately 384 million cases of COPD in 2010 worldwide, which translates as a prevalence of 11.7% (CI 8.4-15.0%).[4] Prevalence and mortality numbers are expected to increase, due to increase in smoking habits in developing countries, and due to ageing of the population in high-income countries.[5]

Several well-known modifiable risk factors for NCDs are associated with an unhealthy lifestyle: tobacco smoking, physical inactivity, excessive use of alcohol, and unhealthy diets including high salt intake. Also air pollution and socio-economic status are associated with NCDs. People from lower socio-economic status are disadvantaged concerning NCDs,[6] since a lower socio-economic status is associated with a higher likelihood to be exposed to harmful factors such as tobacco smoking and unhealthy diet, and to limited access of health services. Most of these risk factors are targeted in the global status report on NCDs by the WHO.[7]

Smoking is the main cause of many respiratory diseases such as lung cancer and COPD, but is also associated with cardiovascular disease (CVD; coronary artery disease (CAD), stroke, congestive heart failure), several other cancers (larynx, pancreas, kidney, etc.),[8] and childhood asthma as well as adult asthma. In addition, smoking is a risk factor for osteoporosis and osteoporotic fractures, reproductive disorders, delayed wound healing, diabetes, and periodontal disease.[8-14] In Europe, there is a decreasing trend of smoking prevalence,[8] but despite governmental anti-smoking campaigns and the increasing awareness that tobacco smoking has negative effects on physical health, smoking remains a worldwide problem.

Chronic obstructive pulmonary disease (COPD)

COPD is a heterogeneous syndrome pathophysiologically related to a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). Air trapping and surface reduction result in reduction in gas exchange. This traditional concept is recently challenged by disappearance of airways, assessed by CT scanning of the chest.[15,16]

COPD is characterised by persistent symptoms of dyspnoea, cough, or sputum production and airflow limitation. COPD is caused by long-term cumulative exposure to noxious particles and gasses, most often tobacco smoking, but also air pollution due to industry and biomass fuels.[17-20] Other factors, such as occupational exposure,[17,21] genetic factors (such as severe alpha-1-antritrypsin deficiency (AATD)[17,22]), socioeconomic status,[23] and lung development abnormalities can also contribute to COPD development.[24]

Traditionally, as reflected in prior GOLD (Global Initiative for Chronic Obstructive Lung Disease[5,24]) guidelines, COPD severity can be categorised into four stages based on the degree of airflow limitation. Patients are categorised having mild, moderate, severe, or very severe airflow limitation (Table 1.1).

In more recent versions of the GOLD recommendations, COPD severity is based on either dyspnoea (the Modified British Medical Research Council (mMRC) Questionaire, a measure of breathlessness) or health status impairment (CAT™: COPD Assessment Tool), and exacerbation history additional to airflow limitation measured by spirometry (see also Figure 1.1).[5] This method results in classifications A, B, C, or D.

Table 1.1 *Disease severity according to GOLD stages[5,24]*

GOLD stage	**Disease severity**	**FEV_1** (% predicted)	**FEV_1/FVC** (ratio)
GOLD stage I	Mild COPD	$FEV_1 \geq 80\%$ predicted	< 0.70
GOLD stage II	Moderate COPD	$50\% \leq FEV_1 < 80\%$ predicted	< 0.70
GOLD stage III	Severe COPD	$30\% \leq FEV_1 < 50\%$ predicted	< 0.70
GOLD stage IV	Very severe COPD	$FEV_1 < 30\%$ predicted	< 0.70

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; % predicted = percentage of the predicted value of someone with the same age, sex, height and race; FVC = forced vital capacity

In this thesis, we have used the GOLD I-IV classifications since this classification method was used in the recruitment of the subjects for the ECLIPSE (Evaluation of COPD longitudinally to identify predictive surrogate endpoints) study, our main data source.

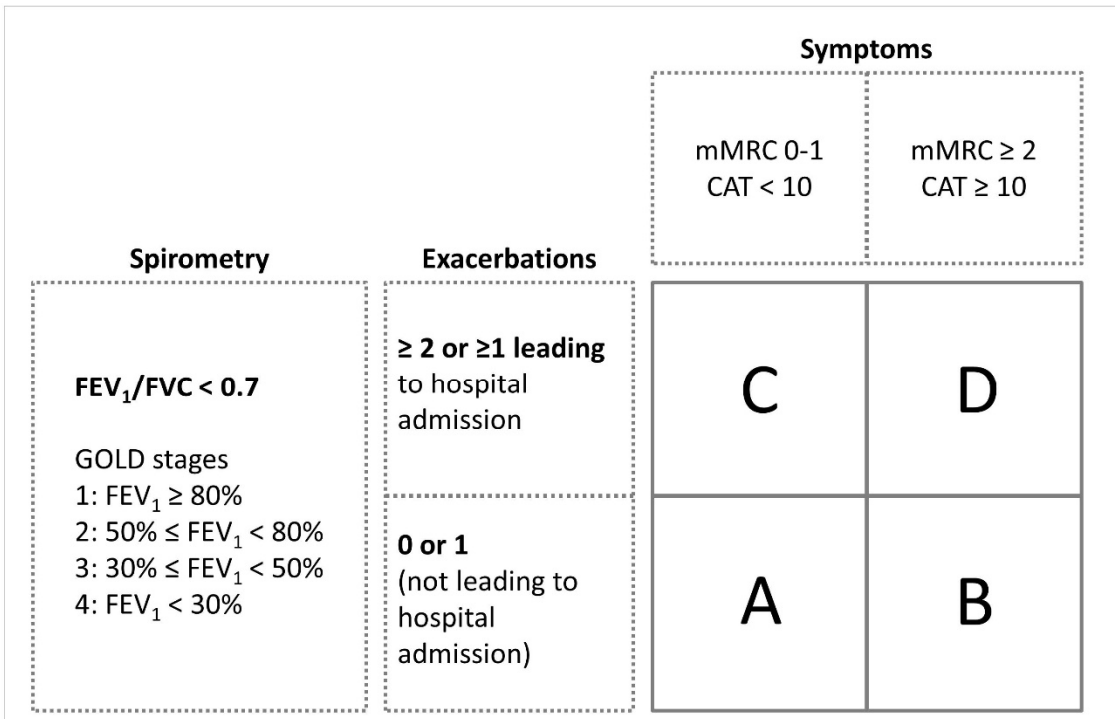

Figure 1.1 *Disease severity refinement by A, B, C, D method, adapted from GOLD guidelines[5] Abbreviations: CAT: COPD Assessment Tool; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; % = percentage of the predicted value of someone with the same age, sex, height and race; mMRC: the Modified British Medical Research Council score*

The socioeconomic burden of COPD on society is high: annual costs directly due to COPD (costs of drugs, patient care, etc.) are estimated to be 23.3 billion euros for the European Union. In addition, indirect costs for example due to absence from work and early retirement are estimated at 25.1 billion.[25] Apart from the economic burden, COPD contributes to disability and mortality.[5]

COPD and comorbidities or multimorbidity

Although COPD is primarily a pulmonary disease, COPD is associated with significant comorbidities and extra-pulmonary disorders such as cardiovascular disease, osteoporosis, diabetes, lung cancer, depression, muscle wasting, anaemia, and gastrointestinal diseases.[26-31] In addition COPD patients more often suffer from general cognitive impairment as compared to control subjects with similar smoking history.[32] Several comorbidities, such as CAD,

depression and lung cancer, have a negative effect on quality of life[30] and are associated with increased risk of mortality.[30,33,34]

Prevalence of comorbidities among COPD patients is reported to be very high[35-37] and comorbid conditions occur irrespective from the degree of airflow limitation.[38] Among 1003 COPD patients, the median number of comorbid conditions was 9 [interquartile range 6-12].[35] In another study 97.7% of 213 COPD patients reported one or more comorbid conditions, while 53.5% reported four or more conditions.[31] Due to the high prevalence and number of comorbidities among COPD patients, COPD nowadays is described as a complex, heterogeneous, multicomponent disease,[38,39] with both pulmonary and extra-pulmonary involvement.[39] Although it is recommended to actively look for comorbid conditions,[24] still only pulmonary symptoms are taken into account to classify disease severity. Using this classification method, the phenotypes within one GOLD-group may still widely vary due to different comorbidities. The variety in intra- and extrapulmonary components result in a heterogeneous and complex disease, which requires multidisciplinary personalised treatment for each individual.[40]

Vanfleteren et al. grouped COPD patients by clustering several major comorbidities to classify more homogeneous subgroups.[31] They have described five comorbidity clusters (less comorbidity; cardiovascular; cachectic; metabolic; and psychologic), emphasizing that certain comorbidities regularly co-exist. Disease severity and inflammatory parameters were comparable between the clusters, but health status was not, once more underlining the clinical relevance of comorbidities. The results of this cluster-approach of comorbidities in COPD patients can be very useful for treatment strategies, and possibly for screening strategies. However, it should be noted that different clustering methods are used in literature, using different statistical methods and different populations (regarding sex, age, smoking history, disease severity), resulting in different patient clusters.[40] In addition, phenotypes might change over time, and therefore patients should be evaluated regularly.

Osteoporosis and vertebral fractures in smokers and patients with COPD

Osteoporosis is a systemic skeletal disease characterised by decreased bone density and microarchitectural deterioration of bone tissue, leading to bone fragility.[41,42] Fractures are the clinical manifestation of osteoporosis, and are typically observed in the hip, spine, and wrist.[41]

According to the WHO definition, osteoporosis is diagnosed based on bone mineral density (BMD) measurements at the spine and/or hip by dual-energy X-ray absorptiometry (DXA). The BMD outcome is expressed in T-scores: standard deviations (SD) in relation to a reference population (young, healthy adult). Osteoporosis is defined as a BMD T-score of -2.5 or lower at the hip, femoral neck, or lumbar spine.[43,44] Osteoporosis can be treated with medication that suppresses bone resorption, such as bisphosphonates and denosumab, or with medication that

stimulates bone formation such as teriparatide and romosozumab.[45-47] However, due to lack of symptoms, osteoporosis often is not diagnosed until after the first fracture.

Risk factors for osteoporosis are older age, immobility, non-Hispanic white or Asian race, a family history of osteoporosis, and for females oestrogen deficiency following menopause or hysterectomy.[48,49] Many diseases and medications can cause osteoporosis.[50] Also lifestyle factors such as smoking, excessive alcohol consumption, malnutrition and inactivity can increase the risk of osteoporosis.

A vertebral fracture (VF), one of the most common osteoporotic fractures,[51-53] is characterised by a collapsed vertebral body resulting in height loss. The grading system by Genant et al.[54] categorizes vertebral fractures into wedge-shaped, biconcave-shaped or crush-shaped VFs based on location of height loss of the vertebral body (anterior, middle, or posterior/total resp.) and into grade 1 up to 3 based on the amount of height loss (20-25%, 25-40%, or ≥40% resp., see Figure 1.2).

Only one third of the patients with a VF present with an acute, symptomatic episode[55] and therefore VFs often go undiagnosed.[56,57] The presence of VFs is associated with increased morbidity, such as back pain, height loss,[58] and change in posture,[59,60] increased risk for subsequent non vertebral[61-64] and vertebral[62,64,65] fractures and mortality.[66,67]

The gold standard for VF diagnosis is lateral radiography. However, also other imaging methods such as lateral imaging of the spine with DXA, computed tomography (CT) or magnetic resonance imaging (MRI) can be used in clinical practice and/or research settings. Although the possibility of opportunistic identification of VFs on DXA and the agreement with lateral radiography of the spine is known in literature,[68] the agreement between the diagnosis of VFs on CT with gold standard X-ray images and DXA is largely unknown.

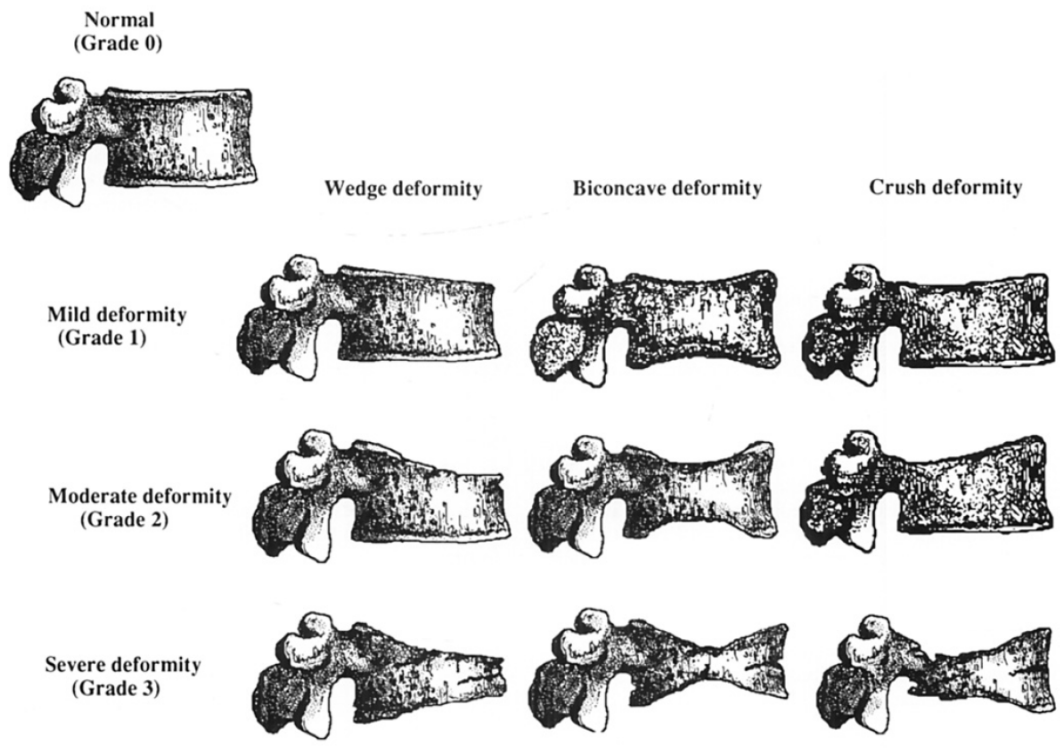

Figure 1.2 *The method of Genant for vertebral fracture grading (image from Genant et al., JBMR 1993)*[54]

Several studies showed that COPD patients are at increased risk of osteoporosis and VFs, due to common risk factors (older age, smoking history,[9,10,69] inactivity,[69,70] body composition[69-73]) and to disease specific risk factors such as systemic inflammation,[74-77] glucocorticosteroid (GC) therapy, [69,71,75,78] hypogonadism[69] and vitamin D deficiency.[69,75,78] Even though it is known that COPD patients are at increased risk, osteoporosis often goes untreated[79] and VFs often go undiagnosed despite evaluable thoracic vertebrae when pulmonary imaging is performed.[80] Most likely VFs are missed partly because they are not often suspected, and partly because the primary focus of these images is pulmonary. The reported prevalence of VFs among COPD patients varies from 9 to 79%,[11,12,79,81-90] depending on factors such as age, sex, race, and GC use. Incidence of VFs among (former) smokers and COPD patients is largely unknown.

VFs lead to height loss and increase in kyphosis, and are a strong risk factor for incident VFs[65,91-94] and non-vertebral fractures.[92,93] Although evidence is limited,[95] the common belief is that VFs and kyphosis influence pulmonary function, which is undesirable especially in patients with already limited pulmonary function such as COPD patients.

While thoracic kyphosis may increase as a consequence of VFs, also ageing, intervertebral disk degeneration and muscle weakness contribute to increased kyphosis.[96] Increase in thoracic kyphosis leads to changes in the loading of the spine, and it was demonstrated in a computational model that loading in the vertebral bodies increases with increasing kyphosis

angles.[97] Whether a greater kyphosis angle is an independent determinant for VF risk is not clear; results in literature are inconsistent on this subject.[98,99]

It has been reported that VFs occur at 'preferential locations' in the mid-thoracic (T_7-T_8) and thoracolumbar (T_{11}-T_{12}) regions of the spine.[53,100,101] These regions have been shown to be the regions at highest load during daily activities such as bending and lifting objects,[102-104] which suggests that VFs occur most frequently in higher biomechanically compromised areas than elsewhere in the spine. It has been shown that prevalent VFs in the upper spine were more related to low bone density than VFs in the lower spine,[105,106] raising the possibility that VFs in the thoracic spine are more reflective of osteoporosis than VFs in the lower spine.

Clustering of osteoporosis and VFs with other comorbidities in COPD

As mentioned before, multiple comorbidities are common among COPD patients and can be clustered. When looking at the clusters as described by Vanfleteren et al., osteoporosis is most common in the 'cachectic' cluster.[31] In addition to high prevalence of osteoporosis (52%), this cluster is characterized by higher prevalence of underweight, muscle wasting, and renal impairment, but lower prevalence of obesity and atherosclerosis compared to the other clusters. The cachectic cluster included a higher proportion of women and current smokers, had on average more static hyperinflation, and a lower cardiovascular risk prediction score. Divo et al. used a network-based analysis to find associations between comorbidities in COPD patients.[107] This analysis showed that osteoporosis was associated with breast cancer, connective tissue disease, restless leg syndrome, hypogonadism, gastro-oesophageal reflux disease, and degenerative joint disease.

Neither of these clustering techniques showed a clear association between osteoporosis and cardiovascular disease among COPD patients, while Laroche et al. suggested that routine osteoporosis evaluation in patients with cardiovascular disease (CVD) could be beneficial based on associations between these two diseases found previously.[108]

CVD is a well-known comorbidity that contributes to mortality in COPD patients.[109] One of the major CVDs is coronary artery disease (CAD). Coronary artery calcification (CAC), assessed by thoracic CT scans, is associated with increased risk of cardiovascular events.[110]

Although it was reported that the highest osteoporosis prevalence (52% in the cachectic cluster of Vanfleteren et al.[31]) was associated with a relatively low cardiovascular risk, the cardiovascular cluster showed the second highest prevalence of osteoporosis (37%).[31] Whether associations between CVD or CAC and osteoporosis or VFs are also present in smokers is unknown.

Systematic assessment of bone attenuation and vertebral fractures on chest CT scans

Chest CT scans are regularly made in patients with COPD and for other pulmonary indications. Besides the primary evaluation, these scans could be used for the evaluation of muscle mass,[111,112] subcutaneous fat,[113] and CAC. It was also reported that opportunistic assessment of bone attenuation (BA), using CT scans obtained for other reasons, could attribute to the detection of osteoporosis,[114] with good correlations between BA on chest CT and BMD on DXA.[115] Also in patients with COPD, strong correlations between BA measured on routine chest CT and BMD assessed on DXA have been reported.[116]

Sagittal reconstructions of chest CT images can also be used for detection of thoracic vertebral fractures. In clinical practice, the diagnosis of vertebral fractures is often based on X-ray or lateral DXA images, but radiological reports on diagnosed vertebral fractures deformities may not always be congruent[117-120] and in literature comparisons of VF detection between imaging modalities mostly concern DXA and X-ray images. In addition, data about vertebral fracture detection when comparing CT scans with DXA and X-ray are sparse, especially regarding the number and severity of vertebral fractures.

The ECLIPSE study

The data presented in this thesis are primarily obtained from the ECLIPSE study (Evaluation of COPD longitudinally to identify predictive surrogate endpoints). The ECLIPSE study is a non-interventional multicentre international study following patients with COPD over three years, to search underlying mechanisms of disease progression in subjects with COPD, and to identify biomarkers that may serve as surrogate endpoints and therefore could measure disease progression (Clinicaltrials.gov identifier NCT00292552; GlaxoSmithKline study SCO104960).[38,121,122]

The ECLIPSE study included COPD patients aged between 40 and 75 years old, with moderate to very severe COPD (GOLD II-IV, i.e. subjects with FEV_1 < 80% predicted and FEV_1/FVC < 0.70). All COPD patients were current or former smokers, with a smoking history of at least 10 pack years (1 pack year = 20 cigarettes per day for 1 year). In addition, control subjects also aged between 40 and 75, with a smoking history (current or former smokers with a smoking history of at least 10 pack years, or non-smokers with < 1 pack years) were included.

This ECLIPSE study population, consisting of (former) smokers with or without COPD is eminently suited for opportunistic screening; COPD is as a complex, heterogeneous, and currently more and more a multimorbid disease. In addition, also (former) smokers are at increased risk of NCDs such as lung cancer, osteoporosis, and CVD and are an interesting population for screening programs.[10,123,124]

A unique feature in the ECLIPSE study is that chest CT scans were obtained at baseline, at one-year and three-year follow-up with CT scanners that were used in clinical practice. For this

thesis we systematically evaluated BA and VFs on the baseline, one-, and three-year follow-up chest CT images among the participants with and without COPD of the ECLIPSE study.

Aims of the thesis

In this thesis we aimed to study the associations between clinical determinants such as age, sex, smoking status, smoking history, CT-measured BA and thoracic kyphosis with prevalent and incident VFs. Additionally, we aimed to study the associations between BA and VF location and the association between VFs and CAC in this specific population.

Outline of the thesis

We first examined the level of agreement for diagnosis of VFs on chest CT scans, lateral DXA images and lateral X-ray images as gold standard (**chapter 2**). Subsequently we systematically studied the prevalence and three-year incidence of VFs in smokers with and without COPD based on chest CT images from the ECLIPSE study participants (**chapter 3**).

We further studied the association between BA and prevalent VFs on chest CT scans and the risk of incident VFs in the ECLIPSE population (**chapter 4**). In **chapter 5**, the association between prevalent VFs and severity of thoracic kyphosis was studied, as well as the association between thoracic kyphosis angles and incident VFs. In **chapter 6** we additionally assessed whether there are predilection locations of prevalent VFs, and whether this was associated with BA of individual vertebrae. In **chapter 7** we evaluated the association between VFs and CAC in a subpopulation of the ECLIPSE study.

To conclude, the overall findings are discussed in **chapter 8**.

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Chapter 2

Diagnosis of vertebral deformities on chest CT and DXA compared to routine lateral thoracic spine X-ray

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Abstract

Summary - X-ray, CT and DXA enable diagnosis of vertebral deformities. For this study, level of agreement of vertebral deformity diagnosis was analysed. We showed that especially on subject level, these imaging techniques could be used for opportunistic screening of vertebral deformities in COPD patients.

Introduction - X-ray and CT are frequently used for pulmonary evaluation in patients with chronic obstructive pulmonary disease (COPD) and also enable to diagnose vertebral deformities together with dual-energy X-ray absorptiometry (DXA) imaging. The aim of this research was to study the level of agreement of these imaging modalities for diagnosis of vertebral deformities from T_4 to L_1.

Methods - Eighty-seven subjects (mean age of 65; 50 males; 57 COPD patients) who had X-ray, chest CT (CCT) and DXA were included. Evaluable vertebrae were scored twice using SpineAnalyzer™ software. ICCs and kappas were calculated to examine intra-observer variability. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the receiver operating characteristic curve (AUROC) were calculated to compare vertebral deformities diagnosed on the different imaging modalities.

Results - ICCs for height measurements were excellent (> 0.94). Kappas were good to excellent (0.64–0.77). At vertebral level, the AUROC was 0.85 for CCT vs. X-ray, 0.74 for DXA vs. X-ray and 0.77 for DXA vs. CCT. Sensitivity (51%–73%) and PPV (57%–70%) were fair to good; specificity and NPV were excellent (≥ 96%). At subject level, the AUROC values were comparable.

Conclusions- Reproducibility of height measurements of vertebrae is excellent with all three imaging modalities. On subject level, diagnostic performance of CT (PPV 79–82%; NPV 90–93%), and to a slightly lesser extend of DXA (PPV 73–77%; NPV 80–89%), indicates that these imaging techniques could be used for opportunistic screening of vertebral deformities in COPD patients.

Keywords

COPD, DXA, Osteoporosis Screening, Vertebral deformity, Vertebral fracture

Introduction

There is an increasing awareness of the risk of vertebral fractures (VFs) in patients with chronic obstructive pulmonary disease (COPD); nevertheless, COPD-associated osteoporosis is largely undertreated.[1]

The reported prevalence of VFs in elderly subjects varies from 5.0% up to 17.8%,[2,3,4] depending on factors such as age, sex and race. Among patients with COPD, the prevalence of VFs is even higher, ranging from 26.8% up to 79.4%.[5,6,7,8,9,10]

Presence of VFs is associated with increased morbidity, such as back pain, height loss,[11] change in posture, [12,13] increased risk for subsequent non-vertebral[14,15,16,17] and vertebral[15,17,18] fractures and mortality.[19,20] Presence of VFs is also associated with respiratory function in COPD patients[1,10] as well as in patients without known lung diseases.[21] More specifically, Watanabe et al. found an association between the presence of VFs and the ratio between forced expiratory volume in 1 s and forced vital capacity (FEV_1/FVC) and between VF severity and FVC[10] in patients with COPD.
Even though VFs occur in a substantial proportion of the elderly population, they are often undiagnosed[22] due to the absence of high impact trauma and lack of typical signs and symptoms of an acute fracture.

Chest X-ray and computed tomography (CCT) of the chest are regularly performed in clinical practice for pulmonary evaluation in COPD patients. Vertebral deformities can be diagnosed on X-ray and CCT images and also on lateral dual-energy X-ray absorptiometry (DXA) images. In clinical practice, these three imaging techniques are often applied in COPD patients, but radiological reports on diagnosed deformities may not always be congruent.[23,24,25,26]

Comparisons between imaging modalities found in literature mostly concern DXA and X-ray images. In a systematic review, Lee et al.[26] concluded that in general, sensitivity is modest and specificity is high when comparing deformities on DXA to X-ray. Takada et al. compared deformities on CT lateral scout views to X-ray[24] and showed good agreement in the total thoracolumbar area (T_4-L_4), with best agreement in the lumbar part of the spine (L_1-L_4).

Data about the comparison of vertebral deformities on DXA and X-ray are sparse, and to our knowledge, there is no study yet regarding the number and severity of vertebral deformities when comparing the three imaging modalities.

Therefore, the aim of this research was to study the level of agreement of these imaging modalities for diagnosis of vertebral deformities from T_4 to L_1.

Methodology

Subjects

For this study, we used data of subjects included in a clinical trial related to osteoporosis in COPD patients (NCT01067248) at the Catharina Hospital (Eindhoven, the Netherlands) between February 2010 and September 2011 (approved by medical ethical committee of the Catharina hospital, M09-1971). The purpose clinical trial was to investigate the pathophysiologic mechanism of osteoporosis in COPD.[27]

Details of the clinical trial as well as inclusion and exclusion criteria were described elsewhere.[27] In short, Caucasian males and postmenopausal females aged 50 years or older with moderate to very severe COPD (classified according to the Global Initiative for Chronic Obstructive Pulmonary disease, GOLD[28]), with either osteoporosis or normal BMD (based on lowest T-score of the lumbar spine (L_1-L_4), femoral neck and total hip), and either with or without vertebral deformities were included, as well as age-matched subjects without COPD.

For the purpose of this study, only subjects with complete availability of an X-ray, a CCT and a DXA with lateral imaging of the spine were included for this study.

Imaging

Lateral X-ray images of the thoracic spine (the current gold standard for assessment of vertebral deformities according to the Dutch guidelines[29]) were obtained by digital radiography (exposure at 125 kV; Digital Diagnost, Philips Health Care, Eindhoven, the Netherlands).

Lateral DXA images of the spine were obtained using a Hologic Discovery A (S/N83295) DXA scanner (Hologic, Tromp Medical Engineering BV, Castricum, the Netherlands). Both X-ray and DXA images were digitally available as Dicom files.

CCT scans of the chest were obtained using either a Philips Brilliance 64 (slice thickness 1 or 0.625) or a Philips iCT 256 scanner (slice thickness 1.25) (both 120 kVp, 350-mm field of view; Philips Health Care, Eindhoven, the Netherlands). To combine information of the sagittal reformats and to mimic the visualisation of the vertebrae on X-ray and DXA, all sagittal reformats containing the spine were superposed into one image: contrast was adjusted in the reformats to (partly) eliminate soft tissue, after which the sagittal reformats were superposed to create simulated X-ray images based on CCT using Matlab version R2013a (MathWorks®).

Vertebral deformity assessment

For morphometric assessment of height loss at posterior, middle and anterior site, SpineAnalyzer™ software (Optasia Medical, Cheadle, UK) was used. This software semi-automatically detects the vertebral shape (height and deformation) on lateral X-ray[30] or DXA[31] images based on user indicated points centred in the vertebrae. Details about the methodology were described elsewhere.[30,31] All of the automatically detected points of the six-point morphometry were manually checked and adjusted if necessary, to make sure the height measurements were in accordance with human interpretation of the image (i.e. no diagnosis of vertebral deformities due to fusion of adjacent vertebrae or Schmorl's nodes). Vertebrae that were not evaluable because of anomalies or other deformities were not included in the analyses. Since deformations were scored based on height measurements and not all qualitative features of morphology were taken into account while grading the deformations, we measured vertebral deformities rather than vertebral fractures.

Based on the measured amount of height loss, the vertebrae were scored according to the cut-off values for vertebral height loss according to the method initially described by Genant et al.[32] as no deformity (height loss < 20%: grade 0), mild deformity (20% ≤ height loss < 25%: grade 1), moderate deformity (25% ≤ height loss < 40%: grade 2) or severe deformity (height loss > 40%: grade 3).

Outcome measures automatically generated by SpineAnalyzer were absolute height (at posterior, middle and anterior site), deformity in percentage (wedge, biconcave, crush) and deformity grade (0–3).

For all image modalities (X-ray, CCT and DXA), vertebrae between T_4 and L_1 were evaluated by one experienced operator (MvD). The operator was trained to apply SpineAnalyzer software by a medical consultant of the software company. All images from one modality were assessed in random order. If all images from one modality were scored, the next modality was scored, again in random order. The second round of evaluation took place with at least 6 weeks in between repeated measures to exclude the change of a recall bias of the previous evaluation round.

To compare the number and severity of vertebral deformities on different image modalities, average heights at the posterior, middle and anterior site were calculated based on the two evaluation rounds. Based on the calculated average heights, deformity in percentage was calculated, resulting in deformity grades (0–3).

After scoring of the individual imaging modalities, the images were compared between modalities to cross-check vertebral levels. In case of discrepancy, a correction was made in vertebral levels based on anatomical landmarks visible in both images, in order to make sure the levels of vertebrae were matched when comparing the different imaging modalities.

Statistics

Since SpineAnalyzer was validated for X-ray and DXA images, but not yet for CCT-based images, we calculated intraclass correlation coefficients (ICC; two-way random, absolute agreement, single rater) for absolute height measurements (posterior, middle and anterior) for all three imaging modalities. Kappa was calculated for diagnosing a vertebral deformity regardless of grade (grade 1-3) or deformity grade 2-3. Kappa and ICC values were interpreted according to Cicchetti et al.:[33] below 0.40, the level of clinical significance was poor; between 0.40 and 0.59, it was fair; between 0.60 and 0.74, it was good; and equal to or above 0.75, it was excellent.

For comparison of vertebral deformities diagnosed on vertebral level between the three imaging modalities, lateral X-ray images were used as gold standard. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for diagnosing a vertebral deformity regardless of deformity grade, as well as for deformity grades 2 or higher. Furthermore, we calculated sensitivity, specificity, PPV, NPV of diagnosing a deformity on DXA compared to CCT.

In addition, we also calculated the area under the receiver operating characteristic curve (AUROC) to determine how well vertebral deformities can be diagnosed with CCT (compared to X-ray) and DXA (compared to X-ray and CCT). The AUROC was interpreted as a fail for values between 0.50 and 0.60; poor between 0.61 and 0.70; fair between 0.71 and 0.80; good between 0.81 and 0.90; and excellent if the value was above 0.90.

For comparison between the three imaging modalities on subject level, each of the images was scored as a vertebral deformity grades 0, 1, 2 or 3 according to the vertebrae with the highest deformity-grade visible between T_4 and L_1. If not all vertebrae between T_4 and L_1 were clearly evaluable, images were scored according to the vertebrae that were evaluable, i.e. the number of vertebrae evaluated per subject was not necessarily equal between imaging modalities.

All statistical analyses were performed in SPSS 24 (IBM) and MS Excel 2010.

Results

In the original study, 102 subjects were included (67 with and 35 without COPD; 48 with osteoporosis and 54 normal BMD; mean age of 65; 58 males and 44 females). Of those, 87 had complete assessment of X-ray, CCT and DXA of sufficient quality for height measurement of the vertebrae. Characteristics of these 87 included subjects are given in Table 2.1.

X-ray and CCT were made on the same day. The mean time interval with DXA was 157.6 days (standard deviation 166.6 days).

When scoring all vertebrae from T_4 to L_1, there were 766 vertebrae (88% of total) identified for height measurements on X-ray images, 787 (90%) on CCT and 718 (83%) on DXA. There were 593 (68.2%) vertebrae evaluable with all three imaging modalities, of which 50 (8.4%) showed a vertebral deformities grade 1–3 according to X-ray, 53 (8.9%) according to CCT and 45 (7.6%) according to DXA.

The distribution of deformities was not equal among vertebrae. By any method, most vertebral deformities were found in the mid-thoracic (T_7/T_8) and the thoracolumbar (T_{11}/T_{12}) area (Figure 2.1). An example of vertebral deformities diagnosed on the three different imaging modalities can be found in the online supplementary material.

Intra-rater reliability on three different imaging techniques

ICCs showed excellent reproducibility of absolute height measurements for all three techniques (ICC > 0.94; Table 2.2). Kappas for diagnosing a vertebral deformity grade 1–3 or deformity grade 2-3 at vertebral level were good and even excellent for diagnosing deformity grade 2-3 on CCT (Table 2.3).

Table 2.1 *Characteristics of the included subjects*

Characteristics	**Total (*n* = 87)**		**Males (*n* = 50)**		**Females (*n* = 37)**	
Age (years)	64.5	7.1	66.2	6.7	62.3	7.2
Height (cm)	170	10	175	8	163	7
Weight (kg)	76.9	17.6	82.8	16.9	69.0	15.4
BMI (kg/m^2)	26.5	5.2	27.0	5.2	25.7	5.2
FFMI (kg/m^2)	17.3	2.6	18.5	2.4	15.8	1.9
Osteoporosis (yes, *n* (col%)	40	46	21	42	19	51.4
COPD (yes, *n* (col%))	*57*	65.5	34	68.0	23	62.2
GOLD 2 (n (col%))	*42*	*48.3*	*24*	*48.0*	*18*	*48.6*
GOLD 3 (n (col%))	*14*	*16.1*	*10*	*20.0*	*4*	*10.8*
GOLD 4 (n (col%))	*1*	*1.1*	*0*	*0.0*	*1*	*2.7*

Values are reported as mean and standard deviation, unless mentioned otherwise

BMI body mass index, FFMI fat-free mass index, COPD chronic obstructive pulmonary disease, GOLD Global Initiative for Chronic Obstructive Pulmonary Disease, col% column percentage

Table 2.2 *ICC on dual height measurements (posterior, mid and anterior)*

	ICC(2,1), single rater		
	X-ray	**CCT**	**DXA**
Height posterior	0.945	0.957	0.957
Height mid	0.944	0.978	0.964
Height anterior	0.947	0.963	0.959

p < 0.001 for all ICCs

Table 2.3 *Agreement on vertebral deformity score when scoring an image twice*

	Kappa vertebral deformity grades 1–3	**Kappa vertebral deformity grades 2–3**
X-ray (*n* = 776)	0.636	0.664
CCT (*n* = 796)	0.713	0.772
DXA (*n* = 758)	0.699	0.628

p < 0.001 for all kappas

Table 2.4 *Sensitivity, specificity, PPV, NPV and AUROC of diagnosing a vertebral deformity regardless of grade (grade 1–3) on vertebral level and of diagnosing a vertebral deformity grade 2 or higher*

	CCT vs X-ray (*n* = 725 vertebrae)		**DXA vs X-ray** (*n* = 631 vertebrae)		**DXA vs CCT** (*n* = 640 vertebrae)	
	Diagnosing VD grade 1–3 (64 on CCT; 62 on X-ray)	Diagnosing VD grade 2–3 (27 on CCT; 29 on X-ray)	Diagnosing VD gr. 1–3 (46 on DXA; 51 on X-ray)	Diagnosing VD gr. 2–3 (17 on DXA; 25 on X-ray)	Diagnosing VD gr. 1–3 (49 on DXA; 60 on CCT)	Diagnosing VD gr. 2–3 (18 on DXA; 26 on CCT)
Sensitivity	73%	72%	51%	44%	57%	42%
Specificity	97%	99%	97%	99%	97%	99%
PPV	70%	78%	57%	65%	69%	61%
NPV	97%	99%	96%	98%	96%	98%
AUROC	0.85	0.86	0.74	0.72	0.77	0.71
95%CI (AR)	[0.78; 0.92]	[0.76; 0.96]	[0.65; 0.83]	[0.59; 0.84]	[0.69; 0.85]	[0.58; 0.83]
p value (AR)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Abbreviations: VD vertebral deformity; gr. Grade; PPV positive predictive value; NPV negative predictive value; AUROC area under the receiver operating characteristic curve; 95%CI (AR) 95% confidence interval of the AUROC; p value (AR) p value of the AUROC

Agreement between X-ray, CCT and DXA at vertebral level

There were 725 matching vertebrae identified between T_4 and L_1 to compare between CCT and X-ray, 631 vertebrae for DXA and X-ray and 640 for DXA and CCT (Table 2.4).

Sensitivity of diagnosing a vertebral deformity regardless of grade (grade 1–3) was 73% for CCT compared to X-ray, 51% for DXA compared to X-ray and 57% for DXA compared to CCT. For diagnosing moderate or severe deformities (grade 2–3), sensitivity was to 72, 44 and 42% resp.

PPV for vertebral deformities regardless of grade (grade 1–3) was 70% for CCT compared to X-ray, 57% for DXA compared to X-ray and 69% for DXA compared to CCT. PPV was 78, 65 and 61% resp. when looking at grade 2–3 deformities only.

Specificity and NPV were ≥ 97% for all comparisons, for diagnosing deformity grade 1–3 as well as grade 2–3.

The AUROC values were good for CCT compared to X-ray (0.85–0.86) and fair for DXA compared to X-ray (0.72–0.74) or to CCT (0.71–0.77) (Table 2.4).

Table 2.5 *Sensitivity, specificity, PPV, NPV and AUROC of diagnosing a vertebral deformity regardless of grade (grade 1–3) on subject level and of diagnosing a vertebral deformity grade 2 or higher*

	CCT vs X-ray (*n* = 87)		**DXA vs X-ray** (*n* = 87)		**DXA vs CCT** (*n* = 87)	
	Diagnosing VD gr. 1–3 (38 subjects on CCT; 35 on X-ray)	Diagnosing VD gr. 2–3 (17 subjects on CCT; 19 on X-ray)	Diagnosing VD gr. 1–3 (31 subjects on DXA; 35 on X-ray)	Diagnosing VD gr. 2–3 (15 subjects on DXA; 19 on X-ray)	Diagnosing VD gr. 1–3 (31 subjects on DXA; 38 on CCT)	Diagnosing VD gr. 2–3 (15 subjects on DXA; 17 on CCT)
Sensitivity	86%	74%	69%	58%	68%	59%
Specificity	85%	96%	87%	94%	90%	93%
PPV	79%	82%	77%	73%	84%	67%
NPV	90%	93%	80%	89%	79%	90%
AUROC	0.85	0.85	0.78	0.76	0.79	0.76
95%CI (AR)	[0.76; 0.94]	[0.72; 0.97]	[0.67; 0.83]	[0.62; 0.90]	[0.69; 0.89]	[0.61; 0.91]
p value (AR)	< 0.001	< 0.001	< 0.001	0.001	< 0.001	0.001

Abbreviations: VD vertebral deformity; gr. grade; PPV positive predictive value; NPV negative predictive value; AUROC area under the receiver operating characteristic curve; 95%CI (AR) 95% confidence interval of the AUROC; p value (AR) p value of the AUROC

Agreement between X-ray, CCT and DXA at subject level

At subject level, sensitivity of diagnosing subjects with a vertebral deformity grade 1–3 was 86% for CCT compared to X-ray, 69% for DXA compared to X-ray and 68% for DXA compared to CCT. Sensitivity was 74, 58 and 59% resp. for diagnosing vertebral deformity grades 2–3.

PPV was 79% for CCT compared to X-ray, 77% for DXA compared to X-ray and 84% for DXA compared to CCT for all grades of vertebral deformities, and 82, 73 and 67% resp. for vertebral deformity grades 2–3.

Specificity of diagnosing subjects with a vertebral deformity grade 1–3 was 85% for CCT compared to X-ray, 87% for DXA compared to X-ray and 90% for DXA compared to CCT. Specificity was 96, 94 and 93% resp. for subjects with vertebral deformity grades 2–3.

NPV was 90% for CCT compared to X-ray, 80% for DXA compared to X-ray and 79% for DXA compared to CCT and was 93, 89 and 90% resp. when looking at vertebral deformity grades 2-3.
AUROC values were good for CCT compared to X-ray (0.85) and fair for DXA compared to X-ray (0.76–0.78) or to CCT (0.76–0.79) (Table 2.5).

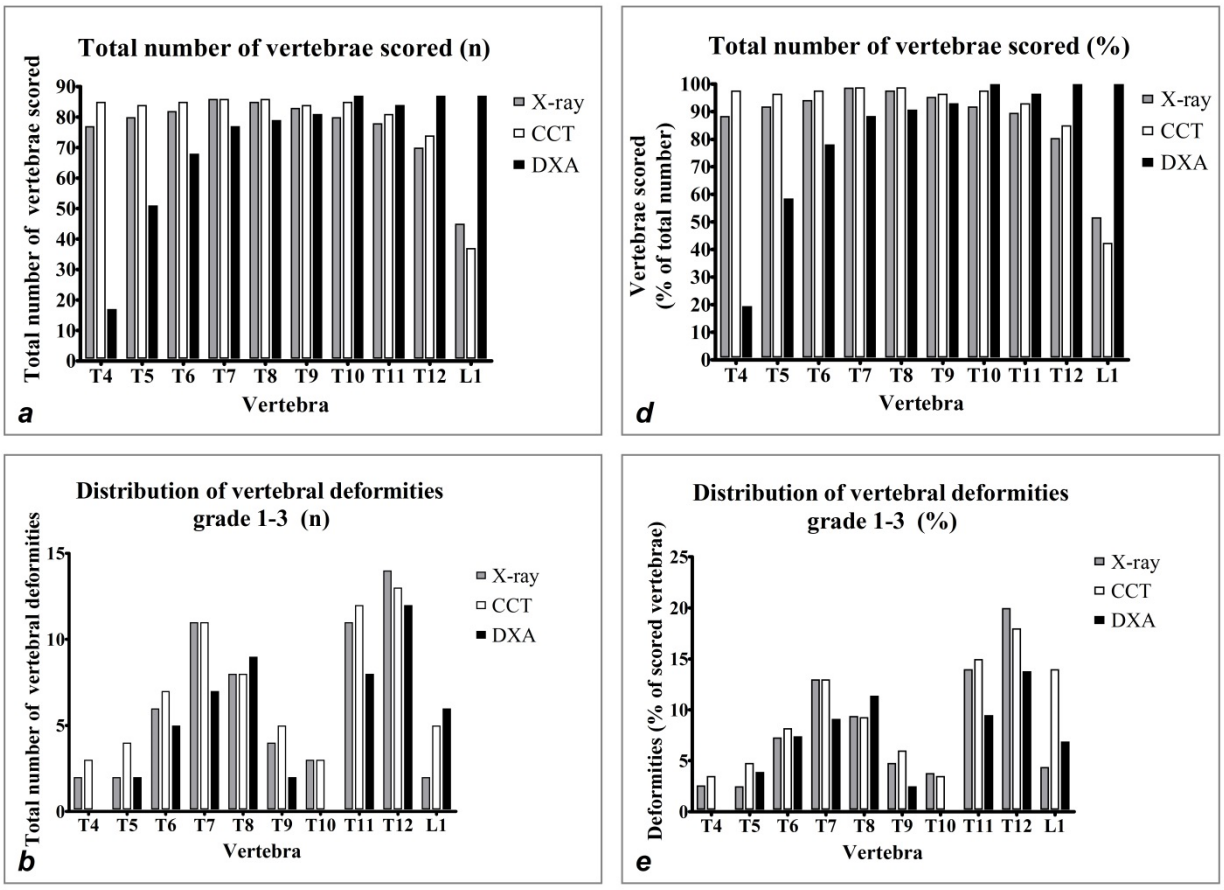

Figure 2.1 *Vertebrae scored and deformities diagnosed on each image modality per location (T_4-L_1) in absolute numbers (**a–c**, maximum = 87) and percentages (**d–f**)*

Discussion

This study showed that reproducibility of height measurement of vertebrae is very good on all three imaging modalities. We also showed that diagnosis of vertebral deformities on vertebral level results in higher sensitivity, PPV, NPV and AUROC value on CCT than DXA when compared to X-ray, but that CCT and DXA showed the same level of specificity. Also on subject level, sensitivity is higher with CCT than with DXA compared to X-ray, except for specificity when looking at vertebral deformity grades 1–3 (85 vs. 87%).

Our reproducibility results for X-ray, CCT and DXA are similar to the results presented by Kim et al.,[23] in which SpineAnalyzer software was used to measure vertebral deformities on CCT lateral scout views.

In literature, there are several studies comparing vertebral deformities diagnosed on DXA to X-ray, mostly from T_4 to L_4, reporting a sensitivity between 57 and 100% and a specificity

between 89 and 100% on vertebral level.[25,34,35,36,37,38,39,40,41] We found comparable specificity (97%) but lower sensitivity (51%) when comparing DXA to X-ray images from T_4 to L_1. Also, on subject level, we found lower sensitivity (69%) but comparable specificity (87%) compared to other studies (sensitivity 69–97%, specificity 74–100%).[34,36,37,38,39,41,42,43,44] One reason could be that most other studies included the lumbar spine in the analysis, in which vertebral deformities are less frequent, while we measured T_4 to L_1. Some studies pointed out that sensitivity and specificity are not uniformly distributed over the spine. In general, sensitivity is lower in the upper thoracic area[39,42,45] due to lower image quality especially in the upper thoracic levels, which may also partly explain the lower sensitivity in our study. On vertebral level, we found the lowest number of grade 1–3 vertebral deformities on DXA images (7.6% of all vertebrae evaluated by all three imaging modalities), followed by X-ray (8.4%) and most vertebral deformities on CCT images (8.9%). Because we found more deformities (grade 1–3) on CCT images, the results suggest that CCT might be a more sensitive method to diagnose vertebral deformities than the current gold-standard X-ray.

We found a modest PPV (57–70%) but a very high NPV (96–97%) on vertebral level. On subject level, diagnostic performance of CT (PPV: 79–82%; NPV: 90–93%) was somewhat better than of DXA (PPV: 73–77%; NPV: 80–89%) compared to X-ray. This suggests that CCT and, to a slightly lesser extent, DXA images made for other medical purposes could be appropriately used for vertebral deformity screening in clinical practice, where DXA has the advantage of lower radiation exposure.

Our study has some limitations.

It should be noted that the subjects in our study population were selected for having either normal BMD or osteoporosis and that a large proportion of this population had COPD. It is expected that COPD patients (65.5% of our study population) and subjects with osteoporosis (46%) have a higher prevalence of vertebral deformities than healthy subjects. Prevalence of a condition (vertebral deformities) does influence PPV and NPV, so our results can only be applied to populations with a similar prevalence of vertebral deformities. However, in populations with high prevalence of vertebral deformities, looking for vertebral deformities on medical images made for other indications is probably of more interest than in low-risk patient groups.

Since DXA scans were performed later than X-ray and CCT, with an average time interval of 157 ± 166.6 days, this could have influenced our results, due to (new) vertebral deformities that may occur within 1 year, especially if subjects already have vertebral deformities.[18]

After recalculation of results with exclusion of 32 resp. 19 subjects with a DXA delay of more than 6 resp. 12 months, no differences were found (data not shown). Therefore, we have no reason to believe that the time interval between DXA and the other two imaging modalities may have influenced sensitivity, specificity, PPV, NPV and AUROC for DXA.

Another limitation is the difference between vertebral fractures and vertebral deformities. When diagnosing vertebral fractures in clinical practice, qualitative features of morphology and medical context should be taken into account. We scored the vertebral deformities based on height measurements using SpineAnalyzer, and although we avoided misclassification of deformities due to fusion of adjacent vertebrae or Schmorl's nodes, we have not taken all qualitative features of morphology and medical context into account. Therefore, we cannot be entirely sure we measured fractures exclusively and no deformations due to degenerative remodelling.

Our main focus of interest was the influence of the different imaging modalities on visualisation of deformations, and therefore, we have chosen to measure deformities rather than only fractures. Whether a mild deformity on an image in clinical setting is an osteoporotic fracture or a deformity of other nature (such as degenerative deformation) should be evaluated by the treating physician, who is familiar with the clinical context.

Lastly, it should be noted that we only investigated vertebrae from T_4 to L_1. In X-ray and CCT images made for pulmonary evaluation, often only the thoracic vertebrae and possibly L_1 are visible and therefore our findings cannot be applied to the lumbar spine.

Conclusion

This study showed that reproducibility of height measurement of vertebrae is excellent with all three imaging modalities. On vertebral level, the NPV is very high but PPV is lower, especially for DXA. On subject level, diagnostic performance of CT (PPV 79–82%; NPV 90–93%), and to a slightly lesser extend of DXA (PPV 73–77%; NPV 80–89%), indicates that these imaging techniques could be used for opportunistic screening for vertebral deformities in patients with COPD.

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Supplementary material

Supplementary Table 2.1 *ICC (intraclass correlation coefficient; two way random, absolute agreement, single rater) on dual deformity (%) measurements (wedge, biconcave and crush)*

	ICC(2,1), single rater		
	X-ray	**CCT**	**DXA**
Deformity wedge	0.767	0.835	0.748
Deformity biconcave	0.568	0.796	0.561
Deformity crush	0.726	0.817	0.637

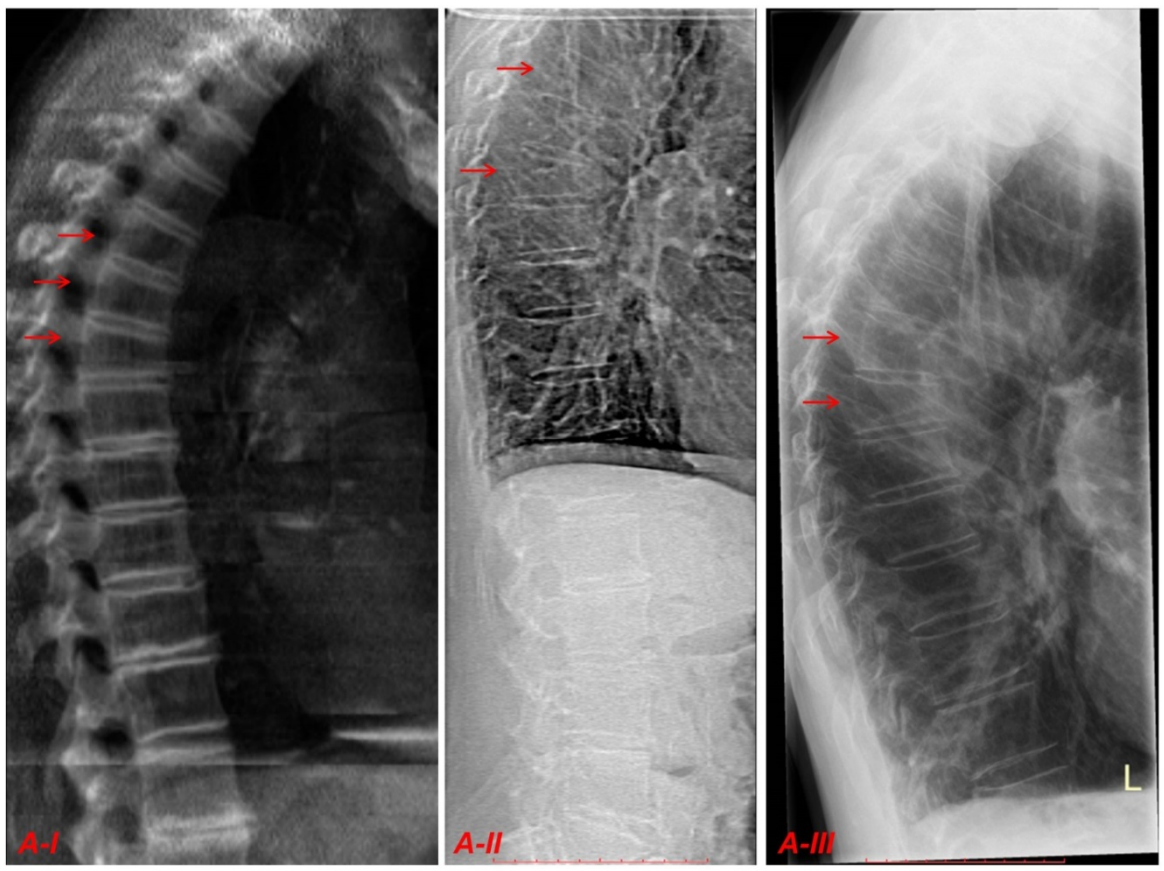
p < 0.001 for all ICC's

Supplementary Table 2.2 *Agreement on vertebral deformity score when scoring an image twice*

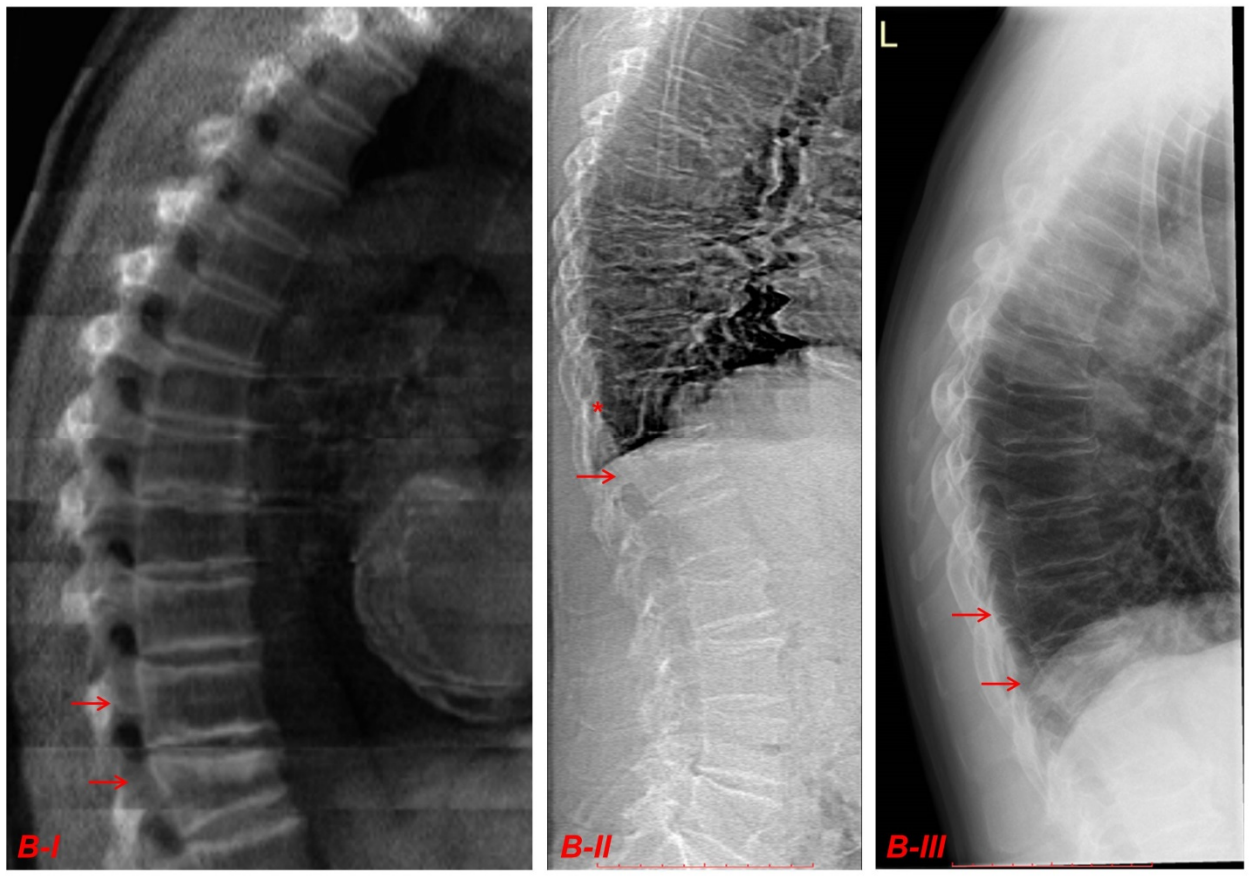
	Weighted kappa* on deformity score
X-ray (n=776)	0.540
CCT (n=796)	0.631
DXA (n=758)	0.581

p<0.001 for all kappa's

**For weighted kappa on deformity score the exact same vertebral deformity score is required to match between evaluation rounds*



Supplementary Figure 2.1a *Examples of vertebral deformities (indicated by red arrows) diagnosed on the three imaging techniques.* ***A)*** *A patient with two or three vertebral deformities (****A-I*** *CT: T_5 grade 1 (23.6%), T_6 grade 2 (25.5%), and T_7 grade 2 (37.7%);* ***A-II*** *DXA: T_5 grade 1 (21.9%), and T_7 grade 2 (34.4%) (deformation T_6: 13.7%);* ***A-III*** *X-ray: T_6 grade 1 (23.7%), and T_7 grade 2 (38.0%) (deformation T_5: 19.1%))*



Supplementary Figure 2.1b *Examples of vertebral deformities (indicated by red arrows) diagnosed on the three imaging techniques.* ***B)*** *A patient with two vertebral deformities (****B-I*** *CT: T_{11} grade 1 (22.2%), and T_{12} grade 3 (46.2%);* ***B-II*** *DXA: T_{12} grade 2 (37.4%) (*T_{11} missing);* ***B-III*** *X-ray: T_{11} grade 1 (21.8%), and T_{12} grade 2 (32.4%))*

Chapter 3

High imminent vertebral fracture risk in subjects with COPD with a prevalent or incident vertebral fracture

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Abstract

Subjects with chronic obstructive pulmonary disease (COPD) have an increased risk of vertebral fractures (VFs); however, VF incidence is largely unknown. Therefore, the aim of our study was to determine the incidence of new and/or worsening VF in subjects with COPD.

Smokers and subjects with COPD (GOLD II–IV) from the ECLIPSE study with complete set of chest CT scans (baseline and 1- and 3-year follow-up) to evaluate vertebrae T1 down to L1 were included. If a VF was diagnosed on the last scan, detailed VF assessment of the previous scans was performed. VFs were scored according to the method of Genant as mild, moderate, or severe. Main outcome measure was the cumulative incidence of new and/or worsening VF at subject level, within 1 and 3 years.

Of 1239 subjects (mean age 61 years, 757 males [61%], 999 subjects with COPD), 253 (20.5%) had ≥1 prevalent VF. The cumulative incidence of VFs was 10.1% within 1 year and 24.0% within 3 years. After adjustment for age, sex, body mass index (BMI), pack-years, and smoking status, prevalence and incidence were similar between smokers and COPD GOLD stages. Within 1 year, 29.2% of the subjects with a prevalent VF had an incident VF, compared with 5.1% in absence of prevalent VF (hazard ratio [HR] = 5.1; 95% confidence interval [CI] 3.6–7.4) and 58.5% versus 15.0% within 3 years (HR = 3.6; 95% CI 2.9–4.6). The incidence of VF was higher with increasing number and severity of prevalent VFs. Among subjects having an incident VF within the first year, 57.3% had a subsequent VF within the next 2 years.

In this study, more than half of the smokers and subjects with COPD with a prevalent VF or an incident VF within the first year sustained a subsequent VF within 3 years. The 3-year risk was even higher in the presence of multiple or severe prevalent VFs.

Keywords

Osteoporosis, Fracture risk assessment, Screening

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 (industry, biomass fuels).[1-4] COPD is characterized by progressive airflow limitation with symptoms of exertional dyspnoea, cough, and increased mucus production.

Currently, COPD is the fourth-leading cause of death worldwide and is expected to be the third-leading cause by 2030.[5] Although it is primarily a respiratory disease, it also has significant extrapulmonary effects. Commonly known comorbidities include osteoporosis, cardiovascular disease, and muscle wasting, and diabetes, anemia, gastrointestinal diseases, depression, and lung cancer are frequently diagnosed in subjects with COPD.[6-9]

Subjects with COPD have an increased risk of osteoporosis and vertebral fractures (VFs), partly because of concomitant risk factors (older age, smoking history,[10-12] inactivity,[12,13] body composition[12-16]) but also because of disease-specific risk factors such as systemic inflammation,[17-20] glucocorticosteroid (GC) therapy,[12,16,18,21] hypogonadism,[12] and vitamin D deficiency.[12,18,22]

The prevalence of radiographic VFs in subjects with COPD as reported in the literature is varying between 9.0% and 79%,[23-34] with the prevalence of radiographic VFs in subjects with COPD increasing from 32% to 52% in a 3-year time period.[32] However, the incidence of clinical VFs in subjects with COPD was as low as 1.3/1000 person-years[35] to 6% over 2.6 years[36] and 0.5% to 1.0% within 3 years.[37]

Smokers without COPD have lower BMD,[38] an increased risk of VFs,[11, 24,34,38,39] and an increased risk of any osteoporotic fracture.[10,39] The prevalence of radiographic VFs in smokers as reported in the literature varied between 11% and 24%,[34,38] whereas incidence of clinical VFs varied from 3%[40] (30-year follow-up) to 26%[39] (10-year follow-up).

VFs are associated with height loss,[41] less activities in daily living,[41] and increased mortality risk.[42] In addition, the presence of a clinical or radiographic VF is a good predictor of subsequent VFs[43-46] and other osteoporotic fractures,[43,44,47,48] even at short term, then quoted as near-term or imminent fracture risk.

There is thus a high variability in the reported prevalence of radiographic VFs in smokers and subjects with COPD and only limited data on the incidence of VFs in smokers and subjects with COPD.

Our aim was to determine the incidence of new and/or worsening VFs in smokers without COPD and subjects with COPD.

Materials and Methods

Study design and population

The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study is a non-interventional, observational, multicenter study that was started to search underlying mechanisms of disease progression in subjects with COPD and to identify biomarkers that may serve as surrogate endpoints and therefore could measure disease progression (Clinicaltrials.gov identifier NCT00292552; GlaxoSmithKline study SCO104960).

Detailed inclusion and exclusion criteria were described elsewhere.[49-51] First, current or former smokers with COPD (40 to 75 years old) with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II (moderate: 50% ≤ forced expiratory volume in 1 second [FEV_1] <80% predicted, and FEV_1/FVC [forced vital capacity] <0.70), stage III (severe: 30% ≤ FEV_1 <50% predicted, FEV_1/FVC <0.70), or stage IV (very severe: FEV_1 <30% predicted, FEV_1/FVC < 0.70), with a post-bronchodilator FEV_1 of <80% of the predicted value, a post-bronchodilator FEV_1/FVC of ≤0.7, and a smoking history of at least 10 pack-years (1 pack-year = 20 cigarettes per day for 1 year) were included. Subjects with COPD were recruited from the outpatient clinics of the participating centers in Europe, North America, and New Zealand.

Current or former smokers (40 to 75 years old) without COPD (with a post-bronchodilator FEV_1 of >85% of the predicted value, a post-bronchodilator FEV_1/FVC of >0.7) and a smoking history of at least 10 pack-years were also included. This group was recruited through site databases and other methods (advertisements in local newspapers and television/radio stations) where appropriate.

Main exclusion criteria were known respiratory disorders or significant inflammatory diseases other than COPD, severe α1-antitrypsin deficiency, a moderate or severe COPD exacerbation (requiring oral GC treatment, antibiotics, or hospitalization) within the 4 weeks before enrollment, and therapy with oral GC at enrollment.

Measurements

At baseline, 1-year follow-up, and 3-year follow-up, demographic information (including age, sex, height, and weight) were collected.

Chest CT scans

CT scans of the chest (120 kV peak, 40 mAs, 1.00 or 1.25-mm volumetric acquisition, General Electric [GE] or Siemens) were performed at full inspiration, at baseline and at 1-year and 3-year follow-up. CT scanners were calibrated regularly using industry and institutional standards.

Of all sagittal reformats containing the spine, the contrast was adjusted to (partly) eliminate soft tissue. Subsequently, all sagittal reformats containing the spine were superposed to create simulated lateral X-ray 2D images using Matlab version R2013a (MathWorks, Natick, MA, USA) (Supplementary Figure 3.1). Images were exported in DICOM format.

Because of our interest in VFs diagnosed on adapted CT images, we only included subjects with complete availability of CT scans at baseline and 1-year and 3-year follow-up; subjects with one or more missing scans were not included in our study.

Vertebral fracture assessment

The adapted sagittal 2D CT images of the last visit (at 3-year follow-up) were visually assessed for VFs from T_1 to L_1.

A semiquantitative visual grading of vertebral fractures was performed, where vertebrae were graded as deformed or not deformed. Vertebrae with deformations due to qualitative features of morphology such as Schmorl's nodes, Scheuermann's disease, platyspondyly, or fusion of vertebrae were excluded. In case of height loss in the vertebral body at the anterior side, in the middle, or in the total vertebral body without other deformities, vertebrae were subsequently morphometrically assessed using the SpineAnalyzer software (Optasia Medical, Cheadle, UK). This software automatically detects the vertebral shape (height and deformation) on lateral images based on user-indicated points centered in the vertebrae.[52] All of the automatically detected points of the six-point morphometry were manually checked by one operator and adjusted if necessary.

The vertebrae were classified based on height loss at posterior, middle, and/or anterior site, according to the method initially described by Genant and colleagues[53] as no fracture (height loss <20%: grade 0), mild fracture (height loss 20% to <25%: grade 1), moderate fracture (25% to <40%: grade 2), or severe fracture (height loss ≥40%: grade 3).

If one or more VFs were quantitatively identified at the 3-year follow-up scan using SpineAnalyzer, the 1-year follow-up scan was also quantitatively assessed. If VFs were also quantitatively identified at the 1-year follow-up scan, the baseline scan was quantitatively assessed as well.

All images were semiquantitatively and quantitatively analyzed by one experienced reader (MJvD), who knew time sequence of the images and that there was at least one VF on later

scans but who was blinded to patient characteristics and number, location, and severity of fracture(s) on other scans.

All images with one or more VFs on the 3-year scan were additionally assessed by an experienced clinician who was not involved in the primary assessment. In case of any doubt about the nature of the deformity, a second clinician independently assessed the images. Decisions with regard to inclusion or exclusion of vertebral deformities such as Scheuermann's disease, Schmorl's noduli, and platyspondyly were reached by consensus.

Main outcome measure

Main outcome measure was the cumulative incidence of new (from grade 0 to grade 1, 2, or 3) and/or worsening (increase in any VF grade, eg, from grade 1 to grade 2) VFs at subject level, within 1 year and within 3 years from baseline.

Statistical analysis

The following potential confounders were determined at baseline: age, sex, weight, body mass index (BMI), smoking history (number of pack-years), and smoking status (current or former smoker).

Because we only selected subjects with complete set of CT scans, missing data were scarce and subjects with missing data were excluded from the analyses concerning those data.

Regression analysis with Cox proportional hazards models (SAS 9.3, SAS Institute, Cary, NC, USA; PHREG procedure) was used to estimate the risk of incident (new and/or worsening) VFs within 1 and within 3 years after baseline, stratified by having COPD, by GOLD stage, by the presence and number of VFs and by severity of VFs at baseline.

Furthermore, Cox proportional hazard models were used to estimate the risk of subsequent VFs within 2 years, in subjects with an incident (new and/or worsening) VF within the first year of the study, stratified by number of VFs at baseline and by severity of VFs at baseline.

In all statistical models, age and sex were included as potential confounders, and other possible confounders were included if they independently changed the beta-coefficient for having COPD by 5% or more or when consensus consisted within the team of researchers supported by evidence from literature.

Results

Of a total of 2298 ECLIPSE subjects (327 smokers and 1971 subjects with COPD), 1478 subjects had the complete set of CT scans (baseline, 1-year, and 3-year follow-up). Of these, 230 subjects were excluded because of scan quality (noise, missing slices, incorrect slice spacing; n = 156), anatomy (could not identify T_1/vertebral levels, deformation of the spine; n = 14), failure of the method to edit CT scans (slice numbers not in ascending order and/or not starting at 0 or 1, problems with white balance in Matlab, or unclear adapted CT images; n = 60), or use of oral GC at baseline (n = 7). Two subjects were excluded because of vertebral deformities (one subject with platyspondyly and one subject with Scheuermann's disease). See also Supplementary Figure 3.2. In 22 subjects with VFs at 3-year follow-up, one or more individual vertebrae were excluded from the analysis because of other deformations such as Schmorl's noduli, degenerative spondylosis, etc.

Thus, for this study, 1239 subjects (240 smokers and 999 subjects with COPD) were included. Baseline characteristics are given in Table 3.1. No subjects used oral GC at baseline. Oral GC use at 1-year follow-up was reported by 23 subjects (2.3% of the subjects with COPD) and by 47 subjects (4.7%) at 3-year follow-up (16 subjects [1.6%] reported GC use at both 1- and 3-year follow-up).

Prevalence of vertebral fractures

At baseline, 20.5% of the participants had a prevalent VF; 15.8% of the smokers and 21.6% of the subjects with COPD (Table 3.2). After adjustment for age and sex, having at least one VF was not significantly different between smokers and subjects with COPD or between GOLD stages.

A significantly larger proportion of the men had a prevalent VF (24.5% in men versus 14.1% in women, $p < 0.001$), and prevalence of VFs was associated with older age ($p < 0.001$).

Table 3.1 *Baseline characteristics (n=1239)*

	Smokers		Subjects with COPD							
			Total		GOLD II		GOLD III		GOLD IV	
	n = 240		n = 999		n = 468		n = 420		n = 111	
Age (years, mean ± sd)	55.0	8.7	62.8	7.0[a]	62.9	7.2	62.9	6.8	62.2	7.1
Sex (M, n (%))	139	57.9	618	61.9	262	56.0	273	65.0	83	74.8
Weight (kg, mean ± sd)	78.7	14.3	73.9	16.0[a]	75.2	16.1	73.2	15.7	70.9	15.7
Fat free mass (kg, mean ± sd)	55.9	11.7	50.5	12.3[a]	51.3	12.7	49.9	11.9	48.9	11.9
Height (cm, mean ± sd)	172.1	9.1	169.6	9.0[a]	169.3	9.3	169.6	8.8	170.8	8.2
BMI (kg/m^2, mean ± sd)	26.5	4.1	25.6	4.6[b]	26.1	4.5	25.4	4.7	24.2	4.4
FFMI (kg/m^2, mean ± sd)	18.7	2.7	17.4	3.2[a]	17.7	3.2	17.2	3.2	16.6	3.3
FEV_1 (L, mean ± sd)	3.39	0.75	1.39	0.52[a]	1.77	0.46	1.14	0.26	0.72	0.16
FEV_1 (%pred, mean ± sd)	109.4	11.8	49.6	15.7[a]	63.8	8.3	40.5	6	24.8	3.6
FVC (L, mean ± sd)	4.33	0.98	3.13	0.91[a]	3.43	0.92	2.98	0.81	2.41	0.71
FVC (%pred, mean ± sd)	113.9	13.4	89.7	19.4[a]	100.0	15.7	84.7	16.4	65.5	14.9
FEV_1/FVC (%pred, mean ± sd)	101.4	6.6	58.5	14.7[a]	68.8	11.6	51.7	10.3	41.1	8.1
Current smoker (n (%))	153	63.8	371	37.1[a]	184	39.3	156	37.1	31	27.9
Former smoker (n (%))	87	36.3	628	62.9[a]	284	60.7	264	62.9	80	72.1
Packyears (mean ± sd)	31.6	20.2	46.1	25.0[a]	44.9	26.7	46.9	22.8	47.8	25.6
VF(s) at baseline (yes, n (%))	38	15.8	215	21.6[c]	99	21.2	87	20.7	29	26.1

COPD chronic obstructive pulmonary disease; GOLD Global Initiative for Chronic Obstructive Lung Disease; BMI body mass index; FFMI fat-free mass index; FEV_1 forced expiratory volume in 1 second; %pred %predicted; FVC forced vital capacity; VF vertebral fracture

FEV_1, FVC, and FEV1/FVC measured post-bronchodilator

[a]p<0.001 versus smokers without COPD; [b]p<0.005 versus smokers without COPD; [c]p<0.05 versus smokers without COPD

Incidence of vertebral fractures, stratified by presence and severity of COPD

The cumulative incidence of VFs within 1 year was 7.5% among smokers and 10.6% among subjects with COPD (Table 3.3), and after 3 years 20.0% and 24.9%, respectively. After adjustment for age, sex, BMI, pack-years, and smoking status, the risk of incident VF was not significantly different between smokers and subjects with COPD.

Table 3.2 *Prevalence of vertebral fractures among smokers and subjects with COPD at baseline, stratified by number and by severity*

	Smokers (n=240)		**Subjects with COPD**							
			Total (n=999)		**GOLD II** (n=468)		**GOLD III** (n=420)		**GOLD IV** (n=111)	
	n	%	n	%	n	%	n	%	n	%
By number of VFs										
no VFs	202	84.2	782	78.4[b]	367	78.8	333	79.3	82	73.9
1 VF	28	11.7	111	11.1	52	11.2	44	10.5	15	13.5
≥ 1 VF	38	15.8	215	21.6[b]	99	21.2	87	20.7	29	26.1
≥ 2 VF	10	4.2	104	10.4[a]	47	10.1	43	10.2	14	12.6
By severity of VFs										
grade 0	202	84.2	782	78.4b	367	78.8	333	79.3	82	73.9
grade 1	25	10.4	95	9.5	52	11.2	35	8.3	8	7.2
grade 2	13	5.4	87	8.7	34	7.3	38	9.0	15	13.5
grade 3	0	0.0	33	3.3[a]	13	2.8	14	3.3	6	5.4

COPD chronic obstructive pulmonary disease; GOLD Global Initiative for Chronic Obstructive Lung Disease; VF vertebral fracture

[a]p<0.005 versus smokers without COPD; [b]p<0.05 versus smokers without COPD

Missing number of VF at baseline: 2 COPD (2 GOLD II); missing highest VF grade at baseline: 2 COPD (2 GOLD II)

In this multivariate model, age and sex significantly influenced the risk of incident VFs within both 1 and 3 years (age per decade: hazard ratio [HR] =1.36, 95% confidence interval [CI] 1.09–1.64 for 1 year and HR = 1.30, 95% CI 1.13–1.48 for 3 years; men had a higher risk of incident VFs than women: within the first year 12.4% of men versus 6.4% of women had an incident VF [HR = 1.86, 95% CI 1.23–2.82] and 27.6% versus 18.5% [HR = 1.41, 95% CI 1.10–1.82] within 3 years). BMI only significantly changed the 1-year risk (HR = 0.96, 95% CI 0.916–0.997) per BMI unit (kg/m2) (See also Supplementary Table 3.1).

Incidence of vertebral fractures, stratified by prevalent vertebral fractures

Apart from age and sex, the presence of a prevalent VF at baseline was a major risk factor for incident VFs. After 1 and after 3 years, the incidence of VFs was 29.2% and 58.5%, respectively, in subjects with a prevalent VF compared with 5.1% and 15.0%, respectively, in subjects without a prevalent VF (1-year HR = 5.1, 95% CI 3.6–7.4; 3-year HR = 3.6, 95% CI 2.9–4.6; adjusted for age, sex, BMI, pack-years, smoking status, and having COPD) (Figure 3.1, Supplementary Table 3.2).

The incidence of VFs was related to the number and severity of baseline VFs. As an example, the 3-year incidence was 68.4% in subjects with ≥2 VFs at baseline (adj. HR = 4.2, 95% CI 3.2-5.6) and 75.8% of subjects with a grade 3 VF at baseline (adj. HR = 4.3, 95% CI 2.7–6.8).

In this model including prevalent VFs at baseline, none of the confounders was significantly associated with the risk of incident VF, except for sex and the risk of incident VF within 1 year (men compared with women, 1-year HR = 1.57, 95% CI 1.03–2.39; 3-year HR = 1.20, 95% CI 0.93–1.55).

Incidence of subsequent VFs within the 2 years after an incident VF

A total of 124 subjects had an incident VF within the first year. Of these 124 subjects, 57% (71 subjects: 26 without prevalent VFs and 45 with 1 or more prevalent VFs at baseline) had a subsequent VF within the next 2 years (Table 3.4). In these subjects, the incidence of subsequent VFs within the 2 years after an incident VF was not significantly related to the presence, number, and severity of prevalent VFs at baseline.

None of the confounders (age, sex, BMI, pack-years, smoking status, or having COPD) were significantly associated with the risk of incident VFs in the 2 years after an incident VF.

Of the 124 subjects with incident VFs within the first year, 3 subjects (2.4%) reported the use of oral GC at 1-year follow-up. Adding the use of oral GC to the model as a confounder did not influence the results (data not shown).

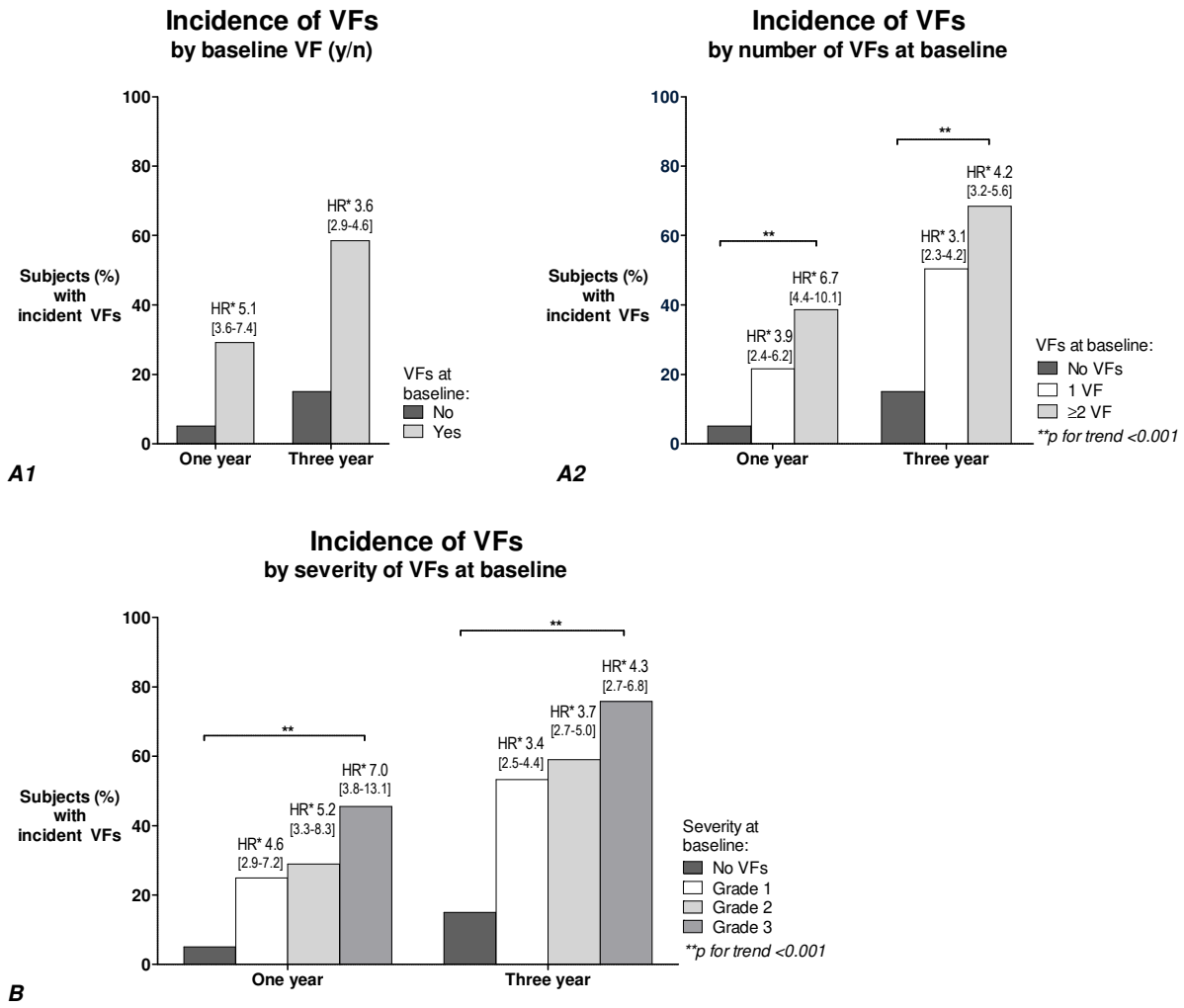

Figure 3.1 *Incidence of vertebral fractures (VFs) and adjusted hazard ratios within 1 and within 3 years, stratified by prevalence (**A1**), by number (**A2**), and by severity (**B**) of VF at baseline*

HR: hazard ratio.
**HR adjusted for age, sex, body mass index, smoking status (current/former), pack-years, and having COPD*

Table 3.3 *Risk of incident vertebral fractures within one and within three years, stratified by COPD and by GOLD stages compared to smokers*

	Incidence within first year		**Risk of incident VFs within first year**				**Incidence within three years**		**Risk of incident VFs within three years**			
	n	%	HR	95%CI	adj. HR	95%CI	n	%	HR	95%CI	adj. HR	95%CI
Smokers (n=240)	18	7.5	-		-		48	20.0			-	
COPD (n=999)	106	10.6	1.4	[0.86-2.34]	1.0	[0.58-1.70]	249	24.9	1.2	[0.92-1.70]	1.0	[0.69-1.35]
COPD by GOLD:												
GOLD II (n=468)	43	9.2	1.2	[0.71-2.14]	0.9	[0.51-1.66]	109	23.3	1.2	[0.83-1.64]	0.9	[0.64-1.33]
GOLD III (n=420)	43	10.2	1.4	[0.79-2.37]	0.9	[0.52-1.68]	106	25.2	1.3	[0.90-1.78]	1.0	[0.66-1.39]
GOLD IV (n=111)	20	18.0	2.4	[1.27-4.54]	1.5	[0.77-3.02]	34	30.6	1.5	[0.99-2.38]	1.1	[0.71-1.81]
			Trend n.s. (p=0.777)		*Trend n.s. (p=0.273)*				*Trend n.s. (p=0.052)*		*Trend n.s. (p=0.617)*	

COPD chronic obstructive pulmonary disease; GOLD Global Initiative for Chronic Obstructive Lung Disease; VF vertebral fractures; HR hazard ratio; adj. HR hazard ratio adjusted for age, sex, body mass index, pack-years, and smoking status; CI confidence interval

Missing first year: 5 subjects with COPD (4 GOLD II, 1 GOLD III); missing 3 years: 2 COPD (1 GOLD II, 1 GOLD III)

Note: the trend for incidence by group is based on "smokers," "GOLD II," "GOLD III," or "GOLD IV"

Table 3.4 *Risk of incident vertebral fractures within the two years, in subjects with an incident vertebral fracture within the first year, stratified by number and by severity of baseline vertebral fractures*

Subjects with incident VFs within first year n = 124							
		Incident VFs within two year follow up		**Risk of incident VF within two year follow up**			
Baseline	n	n	%	HR	95%CI	adj. HR	95%CI
By number of VFs							
no VFs	50	26	52.0			-	
1 VF	30	16	53.3	1.0	[0.55-1.91]	0.9	[0.47-1.74]
≥1 VF	74	45	60.8	1.2	[0.72-1.90]	1.1	[0.62-1.78]
≥2 VF	44	29	65.9	1.3	[0.75-2.15]	1.2	[0.65-2.06]
				Trend n.s. (p=0.38)		*Trend n.s. (p=0.59)*	
By severity of VFs							
no VFs	50	26	52.0	-		-	
grade 1	30	13	43.3	0.8	[0.43-1.62]	0.8	[0.40-1.55]
grade 2	29	19	65.5	1.3	[0.70-2.28]	1.2	[0.62-2.20]
grade 3	15	13	86.7	1.7	[0.86-3.24]	1.6	[0.71-3.38]
				Trend n.s. (p=0.12)		*Trend n.s. (p=0.26)*	

VF vertebral fracture; adj. HR hazard ratio adjusted for sex, age, body mass index, pack-years, smoking status, and having COPD

Note: the trend for incidence by number of VF at baseline is based on "no VF," "1 VF," or "≥2 VF". The group with "≥1 VF" at baseline was excluded from trend analysis.

Discussion

More than half of the current or former smokers and subjects with COPD with a prevalent VF at baseline or an incident VF within the first year sustained a subsequent VF within 2 (after an incident VF) or 3 (after a prevalent VF) years. Three-year incident VF risk was 3.6 times higher in those with a prevalent VF than those without a prevalent VF and independent of age, BMI, and sex (except for a higher 1-year incidence in men). The risk of incident VFs increased with the number and severity of prevalent VFs but was similar between smokers and subjects with COPD and among COPD GOLD stages.

Comparison to published research

The prevalence of VFs in our study population (21.6% of the COPD subjects had ≥1 VF at baseline and 33.5% at 3-year follow-up) was at the somewhat lower range compared with prevalence of most COPD reports found in literature (mostly 24% to 45%,[23-30,32] with outliers of 9.0%[15] and 79.4%[31]). This could probably be explained by the fact that the subjects in this study were not using oral GC at baseline because of study design (subjects using oral GC at baseline were excluded, and only 23 and 47 subjects, respectively, reported oral GC use at 1-year and 3-year follow-up), whereas in most (12% to 86%[15,25-27,29-32] GC use) but not all (2.2% to 4.5%[23,24,28] GC use) studies, the percentage of subjects using GCs was considerably higher.

Furthermore, we measured vertebrae T_1 to L_1 and therefore had no information regarding VFs in the lumbar vertebrae except L_1. McEvoy and colleagues[33] showed that 16.5% of the male COPD patients in their study population had a VF in the lumbar spine and 49.0% in the thoracic spine and that the risk of VFs was highest in patients using GC.

In a large cohort of COPD patients in Italy, Nuti and colleagues[28] found a relationship between COPD severity by means of GOLD stages and prevalence of ≥1 VF, especially in male subjects. In a multivariate model, they showed an association between VFs and age, fracture history after the age of 50 years, BMI, COPD severity, and GC treatment; however, they did not report VF incidence. In our study, we could not show a significant association between prevalence of VFs and GOLD stages (adjusted for age and sex). However, our study population was younger, all subjects had a significant smoking history (mean of 43.3 ± 24.8 pack-years, with a minimum of 10 pack-years), whereas in the study by Nuti and colleagues 13.3% of men and 55.1% of women were non-smokers and subjects with GOLD stage I were not included.

Another remarkable finding was that there was no difference in VF incidence between smokers and subjects with COPD. Our participants had a significant smoking history (46 pack-years for the COPD group, 32 for the smokers), indicating that smoking rather than COPD is a major risk factor for VFs.[11,38,39]

In a group of 90 COPD patients (69 ± 1 years old, 60% male), Graat-Verboom et al.[32] showed an increase of prevalent VFs from 32% to 52% within three years (63% increase). In our study population, prevalence of VFs increased from 20.4% at baseline to 24.5% at 1-year and 32.4% at 3-year follow-up (59% increase), indicating a similar increase.

We showed that presence, number, and severity of prevalent VFs were associated with risk of incident VFs, which is in line with multiple studies showing that prevalent VFs are an important independent risk factor for subsequent VFs[43-45,54] and several other osteoporotic fractures.[43,44,47,48,54] However, the imminent 1-year risk was much higher than reported in postmenopausal women.[45] In postmenopausal women selected on the basis of a prevalent VF, low BMD at the femoral neck, or risk factors for hip fracture, the 1-year VF incidence was 1.9% in women without prevalent VFs, 9.9% in women with prevalent VFs of unknown date, and 19.2% in women with an incident VF.

Given the VF prevalence of 21.6% in COPD subjects and the high risk of subsequent VFs in those with a prevalent or incident VF, we propose to systematically evaluate the presence of VFs when these patients have chest X-ray or chest CTs made for pulmonary evaluation. Improvement in patient care can be achieved by increasing awareness among pulmonologists and radiologists about the clinical importance for recognizing VFs. Patients with VFs should be further evaluated and treated according to local osteoporosis and fracture prevention guidelines.

Limitations

This study has several limitations. First, there is a possibility of a selection bias. Because we only included subjects with complete availability of all three CT scans, we have only selected the surviving subjects and subjects willing and able to complete the study. The subjects included in our subcohort were somewhat younger (61.3 ± 8.0 versus 62.3±7.9 years old), were less often males (61.1% versus 62.6%), had lower BMI (25.8 ± 4.5 versus 26.6 ± 5.5 kg/m2), and were more often smokers without COPD (19.4% versus 14.2%) compared with the total ECLIPSE population. The percentage of current smokers was higher (42.3% versus 39.9%), but the mean number of pack-years was lower (43.3 ± 24.8 versus 46.2 ± 27.1) compared with the total ECLIPSE population (Supplementary Table 3.3).

Second, the subjects in this study, especially those with COPD, were selected based on not using oral GC at baseline, and subjects with COPD were selected from outpatient clinics, which limits the applicability of our results to subjects with COPD in general. Besides, the group including subjects with very severe COPD (GOLD stage IV) was smaller than the other groups (111 compared with 468 subjects with GOLD II and 420 subjects with GOLD III), which possibly may have resulted in a limited statistical power when estimating the association of GOLD stage IV with the risk incident VFs in this specific group.

Furthermore, although 524 (42.3%) of all subjects were current smokers, there was only a limited number of current or former smokers without COPD included in our study (n = 240), which limits the generalizability of these results to the general population of heavy (current or former) smokers without COPD. In addition, the participating research centers were located in North America, Europe, and New Zealand, and therefore the results are not applicable to populations of other ethnic origin.

Although the incidence of VFs within 3 years after a prevalent VF at baseline (148 of 253 subjects, 58.5%) or within 2 years after an incident VF within the first year (26 of 50 subjects, 52.0%) is very high, it should be noted that the sample size of subjects with a prevalent VF (n = 253) or incident VF within the first year in absence of prevalent VFs (n = 50) is limited.

We assessed VFs on images based on CT scans and used morphometry software to assess VFs, which possibly has resulted in a more sensitive method to assess VFs than by visual inspection of X-ray images. In the absence of beam divergence and with use of morphometry software, small height changes can be detected that could have resulted in higher VF grade, thereby possibly making CT in combination with morphometry software more sensitive.

Lastly, we only have assessed VFs between T_1 and L_1 because of the nature of our scans and therefore cannot say anything about prevalence and/or incidence of VFs in the lower lumbar part of the spine. It is possible that not assessing L_2 to L_5 has resulted in an underestimation because of missing prevalent and/or incident VFs in this lumbar area. However, according to literature, most VFs occur in the mid-thoracic and thoracolumbar area of the spine,[55-60] which are both visible on chest CT scans.

In conclusion, in this 3-year follow-up study, we showed that more than half of the heavy current or former smokers and COPD subjects with a prevalent VF at baseline or an incident VF within the first year sustained a subsequent VF within the follow-up period (3 years after a prevalent VF, 2 years after an incident VF). This imminent VF risk was even higher in the presence of multiple or severe VFs at baseline.

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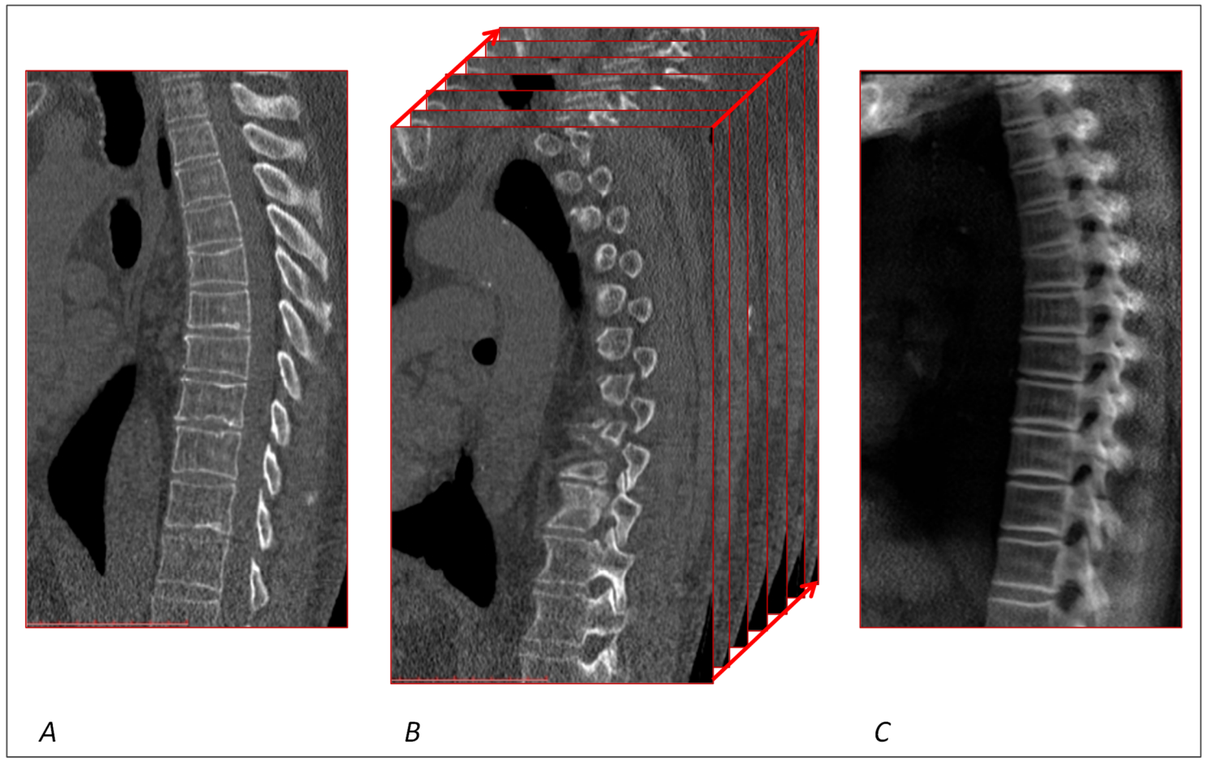
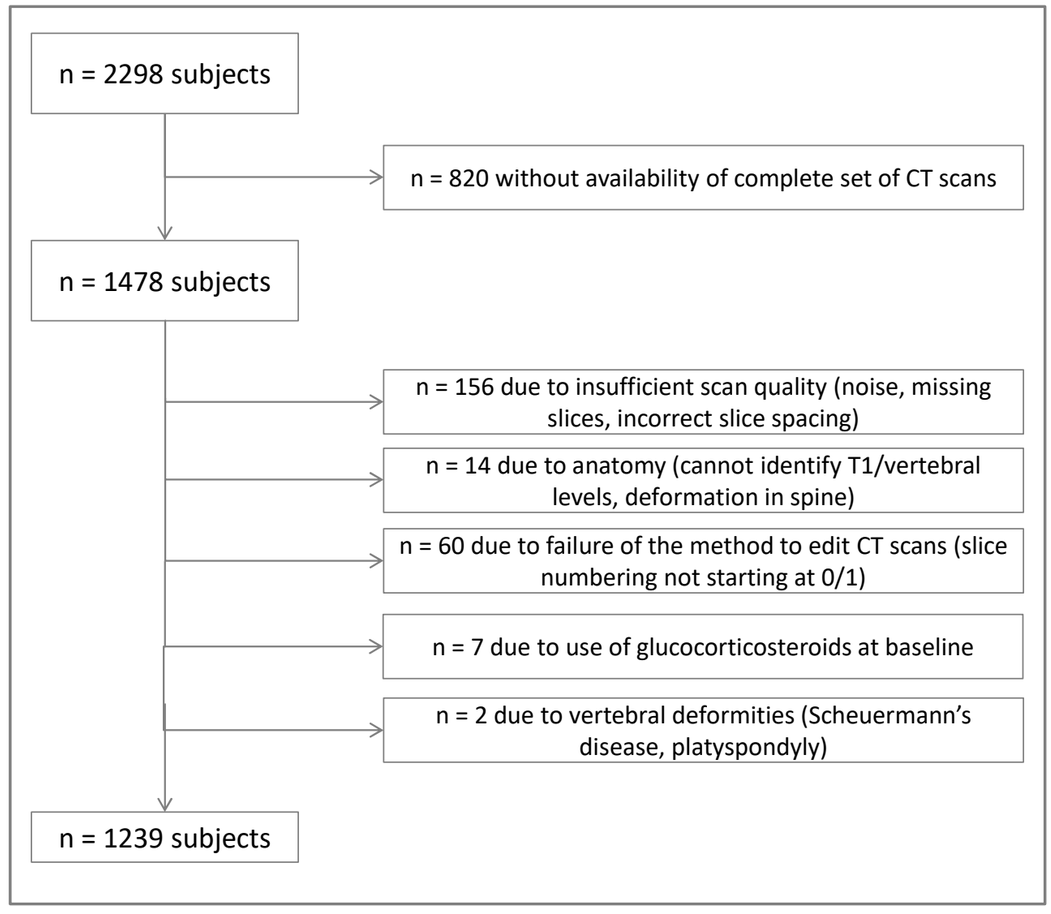
Supplementary material

Additional Supporting Information may be found in the online version of this article. (https://doi.org/10.1002/jbmr.3429)



Supplementary Figure 3.1 *Simulated lateral X-ray images based on CT: (**A**) sagittal reformat centered in the spine (**B**) superposing of all sagittal reformats containing the spine (schematic; not all sagittal reformats shown in image) and (**C**) the simulated lateral X-ray image based on CT*



Supplementary Figure 3.2 *Flow diagram of included subjects*

Supplementary Table 3.1 *Risk of incident vertebral fracture within one and three years, stratified by number and by severity of baseline vertebral fractures*

		Incidence within first year		**Risk of incident VFs within first year**				**Incidence within three years**		**Risk of incident VFs within three years**			
baseline	n	n	%	HR	95%CI	adj. HR	95%CI	n	%	HR	95%CI	adj. HR	95%CI
By number of VFs													
no VFs	984	50	5.1	-		-		148	15.0	-		-	
1 VF	139	30	21.6	4.3	[2.72-6.73]	3.9	[2.45-6.15]	70	50.4	3.3	[2.52-4.45]	3.1	[2.34-4.18]
≥1 VF	253	74	29.2	5.8	[4.07-8.34]	5.1	[3.55-7.44]	148	58.5	3.9	[3.11-4.90]	3.6	[2.85-4.57]
≥2 VF	114	44	38.6	7.7	[5.16-11.59]	6.7	[4.38-10.11]	78	68.4	4.6	[3.49-6.04]	4.2	[3.17-5.58]
				Trend significant (p<0.001)		*Trend significant (p<0.001)*				*Trend significant (p<0.001)*		*Trend significant (p<0.001)*	
By severity of VFs													
no VFs	984	50	5.1	-		-		148	15.0	-		-	
grade 1	120	30	25.0	5.0	[3.18-7.87]	4.6	[2.88-7.24]	64	53.3	3.6	[2.67-4.79]	3.4	[2.49-4.54]
grade 2	100	29	29.0	5.8	[3.65-9.11]	5.2	[3.26-8.27]	59	59.0	3.9	[2.90-5.30]	3.7	[2.71-5.00]
grade 3	33	15	45.5	8.9	[5.02-15.93]	7.0	[3.76-13.13]	25	75.8	5.0	[3.30-7.70]	4.3	[2.74-6.80]
				Trend significant (p<0.001)		*Trend significant (p<0.001)*				*Trend significant (p<0.001)*		*Trend significant (p<0.001)*	

Abbreviations: VFs = vertebral fractures; adj. HR = Hazard ratio adjusted for age, sex, BMI, pack years, smoking status and having COPD

Note: the trend for incidence by number of VFs at baseline is based on 'no VFs', '1 VF', or '≥2 VFs'. The group with '≥1 VF' at baseline was excluded from trend analysis, since this group includes subjects with 1 VF as well as subjects with ≥2 VFs at baseline, and for trend analysis groups should be mutually exclusive.

Missing incidence first year: 5 subjects; missing incidence three years: 2 subjects

Supplementary Table 3.2 *Baseline characteristics of total ECLIPSE population, and of subjects excluded or included in our study*

	Total ECLIPSE n = 2298		**Excluded*** n = 1059		**Included** n = 1239	
Age (years, mean ± sd)	62.3	7.9	63.4	7.7	61.3	8.0
Sex (M, n (%))	1439	62.6	682	64.4	757	61.1
BMI (kg/m2, mean ± sd)	26.6	5.5	27.5	6.4	25.8	4.5
no COPD (n (%))	327	14.2	87	8.2	240	19.4
COPD GOLD stage I (n (%))	2	0.1	2	0.2	0	
COPD GOLD stage II (n (%))	878	38.2	410	38.7	468	37.8
COPD GOLD stage III (n (%))	829	36.1	409	38.6	420	33.9
COPD GOLD stage IV (n (%))	262	11.4	151	14.3	111	9.0
Smoking status:						
Current smoker (n (%))	916	39.9	392	37.0	524	42.3
Former smoker (n (%))	1382	60.1	667	63.0	715	57.7
Pack years (mean ± sd)	46.2	27.1	49.6	29.1	43.3	24.8

*Due to one or more missing scans, scan quality, etc.

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease

Chapter 4

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.

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 death 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 BMD measurements on DXA in a COPD population (r=0.827, p<0.001).[20] Opportunistic use of BA on CT scans for osteoporosis screening and for bone mineral density (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 dual-energy x-ray absorptiometry (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 measure at 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 (stage

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 second, FVC=forced vital capacity, both post-bronchodilator and expressed as % predicted), see also online supplement), or without COPD (FEV_1>85%, FEV_1/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 four 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, one-year and three-year CT scan for this study.

Measurements

At baseline, one- and three-year follow-up, demographic and pulmonary information (FEV_1, FEV_1/FVC) were collected. Also information about smoking behaviour (pack years, current or former smoker) was 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, one- and three-year follow-up. CT scanners were used in daily clinical practice at all participating centres and calibrated regularly using industry and institutional standards.

Vertebral fracture assessment

Detailed information has 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 three-year image, after exclusion of deformities due to Scheuermann's disease, Schmorl's noduli, or platyspondyly. In case of a VF, vertebra 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 one year, or between baseline and three year.

Bone attenuation

BA was measured on CT in regions of interest (ROIs) of approximately 275mm^3 centred 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 Figure 4.1. 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).

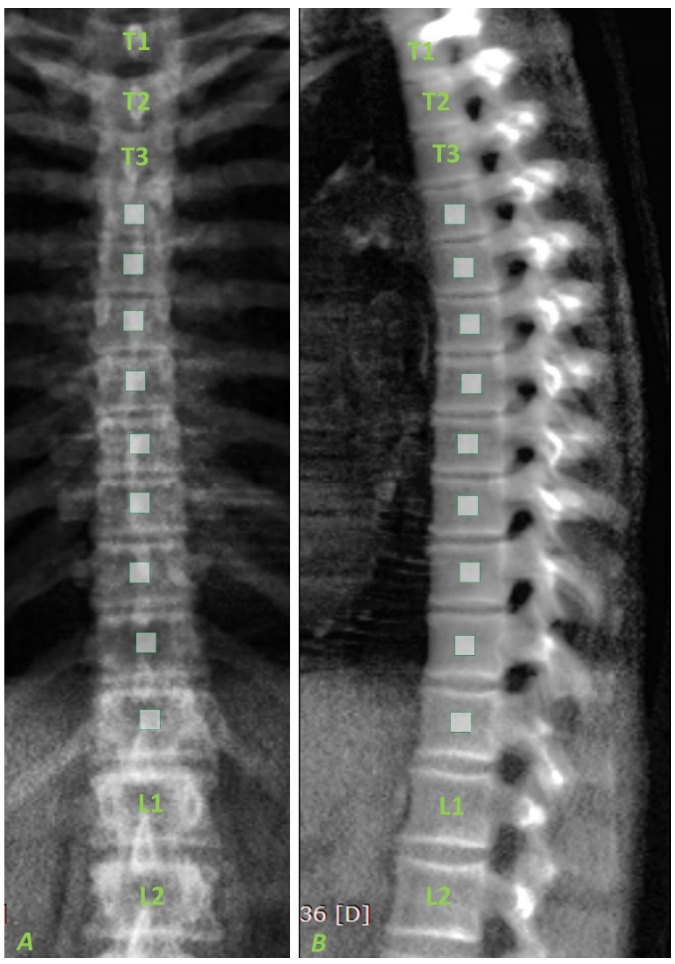


Figure 4.1 *Placement of ROIs in vertebrae T_4-T_{12}: the green-outlined semi-transparent cubes in the images represent the ROIs in vertebrae T_4-T_{12} in which BA was measured*
***A**) frontal and **B**) sagittal view of ROI placement*

Main outcome measures

Main outcome measure was the incidence VFs within one and within three 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 one or within three years were included.

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 was compared using linear and logistic regression models respectively.

Logistic regression analysis (SAS 9.3, SAS Institute, Cary, NC, USA; REG 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 one and three years. The latter was also applied to a subset of subjects without prevalent VFs.

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

In all models, 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, one-year and three-year follow-up). 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 glococorticosteroids (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 4.1), 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 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 4.1).

Table 4.1 *Clinical characteristics*

		All subjects		Subjects without COPD		Subjects with COPD	
		n = 1239		n = 240		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 one year (n, %)		120	9.7	17	7.1	103	10.3
Incident VF within three years (n, %)		296	23.9	48	20.0	248	24.8

Abbreviations: COPD = chronic obstructive pulmonary disease; BMI = body mass index; FFMI = fat free mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HU = Hounsfield Units; VF = vertebral fracture

FEV_1 and FEV_1/FVC both post-bronchodilator

Table 4.2 *Determinants of prevalent vertebral fractures*

	Without prevalent VFs n = 984		**With prevalent VFs** n = 253		**Univariate** OR	95% CL	**Multivariate** OR	95% CL
Age (years: mean, sd) *(HR 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, %) *(HR 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) *(HR 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, %) *(HR vs former)*	434	44.1	89	35.2	0.688	[0.516-0.916]	0.874	[0.626-1.219]
Pack years (mean, sd) *(HR 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) *(HR 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) *(HR 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, %) *(HR 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, %) *(HR vs. no COPD)*	367	37.3	99	39.1	1.434	[0.950-2.163]		
GOLD III (yes: n, %) *(HR vs. no COPD)*	333	33.8	87	34.4	1.388	[0.913-2.112]		
GOLD IV (yes: n, %) *(HR vs. no COPD)*	82	8.3	29	11.5	1.880	[1.088-3.249]		
BA (HU: mean, sd) *(HR 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)

Abbreviations: VF = vertebral fracture; CL = confidence limits; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; 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 both post-bronchodilator

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

At one-year and three-year follow-up, 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 4.2).

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 one year (Table 4.3). Only 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 three years.

When combining information on BA and prevalent VFs, the one-year adjusted HR for subjects with prevalent VFs in the lowest BA tertile was 7.5 [95%CI: 4.1-14.0], and the three-year adjusted HR was 5.4 [3.7-8.1], compared with subjects without prevalent VFs in the highest BA tertile (Figure 4.2).

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 4.4). Baseline BA was the only significant determinant for the risk of incident VFs within three years (per -1SD HR=1.37 [1.12-1.68]).

Table 4.3 *Determinants of incident vertebral fractures within one and three years*

	Without incident VFs		**With incident VFs**		**Univariate**		**Multivariate (with COPD as total)**	
ONE YEAR	n = 1114		n = 120		HR	95% CL	HR	95% CL
Age (years: mean, sd) [a]	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) [a]	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) [a]	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) [a]	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) [a]	67.2	21.7	62.2	21.7	0.80	[0.659-0.972]	1.01	[0.654-1.573]
COPD (yes: n, %) [b]	891	80.0	103	85.8	1.46	[0.875-2.442]	0.57	[0.216-1.481]
GOLD II (yes: n, %) [b]	*422*	37.9	*42*	35.0	*1.28*	*[0.727-2.245]*		
GOLD III (yes: n, %) [b]	*377*	33.8	*42*	35.0	*1.42*	*[0.806-2.486]*		
GOLD IV (yes: n, %) [b]	*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) [a]	-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]		
VFs grade 2/3 (n, %) *(HR vs. no or gr1 VF)*	89	8.0	42	35.0	4.53	[3.116-6.598]		
THREE YEARS	n = 941		n = 296		HR	95% CL	HR	95% CL
Age (years: mean, sd) [a]	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) [a]	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) [a]	42.5	23.9	45.8	27.4	1.10	[0.989-1.220]	1.01	[0.904-1.137]
FEV1 (%pred: mean, sd) [a]	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) [a]	67.5	21.7	64.2	21.5	0.89	[0.785-0.998]	0.97	[0.734-1.275]
COPD (yes: n, %) [b]	749	79.6	248	83.8	1.24	[0.913-1.694]	0.74	[0.409-1.323]
GOLD II (yes: n, %) [b]	*358*	38.0	*109*	36.8	*1.17*	*[0.831-1.639]*		
GOLD III (yes: n, %) [b]	*313*	33.3	*106*	35.8	*1.26*	*[0.899-1.779]*		
GOLD IV (yes: n, %) [b]	*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) [a]	-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]		
VFs grade 2/3 (n, %) *(HR vs. no or gr1 VF)*	49	5.2	83	28.0	3.26	[2.533-4.206]		

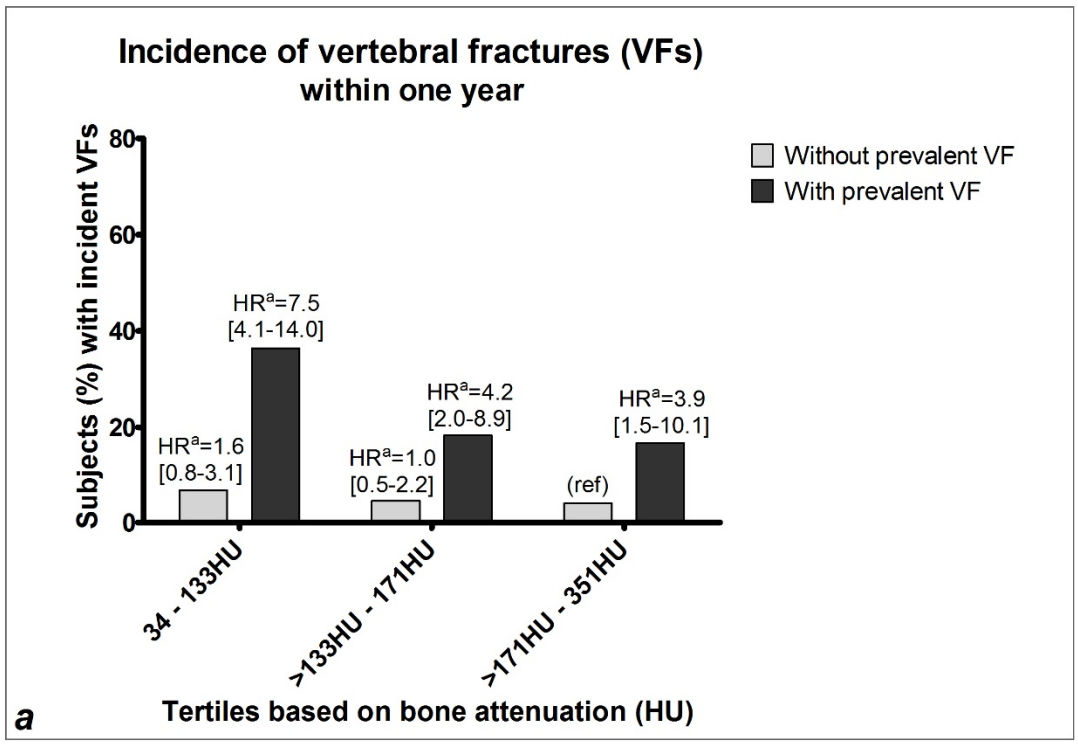
Missing one year: 5 subjects (5 males; 4 GOLD 2, 1 GOLD 3); missing three year 2 subjects (2 males; 1 GOLD II, 1 GOLD III)

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

FEV_1 and FEV_1/FVC 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

[a] *(HR per SD)*
[b] *(HR vs. no COPD)*

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 one year SD = 10 HU; ΔBA three year SD = 14HU



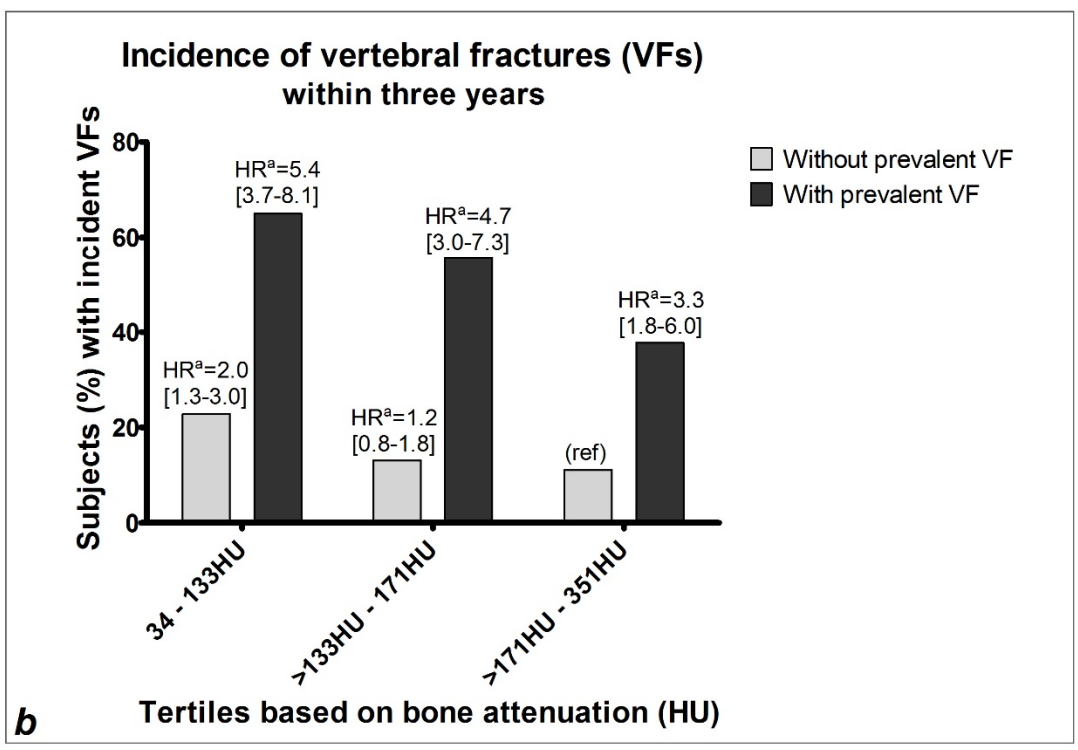


Figure 4.2 *Incidence of vertebral fractures (VFs) within **A**) one year and within **B**) three years, stratified by bone attenuation tertiles (measured in Hounsfield Units (HU)) and prevalence of VFs at baseline*
HR[a] adjusted for age, sex, body mass index, having COPD, pack years, and smoking status
Reference group is highest bone attenuation tertile, without prevalent VFs at baseline

Table 4.4 *Determinants of incident VFs within one and three years in subjects without prevalent VFs*

	Without incident VFs		With incident VFs		Univariate		Multivariate (with COPD as total)	
ONE YEAR	n = 935		n = 49		HR	95% CL	HR	95% CL
Age (years: mean, sd) [b]	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) [b]	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) [b]	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) [b]	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) [b]	67.8	21.7	62.8	21.9	0.79	[0.585-1.069]	0.64	[0.328-1.265]
COPD (yes: n, %) [c]	742	79.4	40	81.6	1.15	[0.557-2.366]	0.24	[0.052-1.074]
GOLD II (yes: n, %) [c]	*353*	37.8	*14*	28.6	*0.86*	[0.371-1.978]		
GOLD III (yes: n, %) [c]	*314*	33.6	*19*	38.8	*1.28*	[0.579-2.830]		
GOLD IV (yes: n, %) [c]	*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) [b]	-2.6	9.6	-1.4	10.6	1.12	[0.846-1.482]	1.03	[0.760-1.403]
THREE YEARS	n = 836		n = 148		HR	95% CL	HR	95% CL
Age (years: mean, sd) [b]	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) [b]	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) [b]	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) [b]	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) [b]	67.8	21.8	66.5	21.7	0.95	[0.806-1.121]	0.88	[0.596-1.285]
COPD (yes: n, %) [c]	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) [b]	-8.7	14.2	-8.0	13.0	1.05	[0.889-1.230]	0.97	[0.821-1.153]

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

FEV_1 and FEV_1/FVC 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

[a] [1.000223-1.780165]
[b] (HR per SD)
[c] (HR vs. no COPD)

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 one year SD = 10 HU; ΔBA three year SD = 14HU

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 one and three years. However, the presence of one or more prevalent VFs was a much stronger determinant for the short-term VFs 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 to apply for 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 increased fracture risk, and for which diagnostic pulmonary CT scans are regularly made.

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 Figure 4.2. The independent additive value of BA and prevalent VFs on incident VF risk is in line with 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 (L1-L3) 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 L1) in subjects with incident fragility fractures, including vertebral fractures.[35]

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 one year (Table 4.4), while only baseline BA was associated with the three-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 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 and157.0 ±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 4.2).

Neither presence of COPD nor disease severity by means of GOLD stage significantly increased 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: 155.5HU; without prevalent VFs: 162.2HU; with prevalent VFs: 128.3HU) were in the same range as 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 general population of smokers with or without COPD. ECLIPSE recruited subjects from outpatient clinics (COPD patients) of 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 full set of three CT scans, i.e. subjects willing to and able to complete the study (see also Supplementary Table 4.1 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 prevalence and incidence of VFs, and may limit the generalizability of the presented results to comparable populations. In addition, several studies have presented 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. ROI size was approximately 275mm^3 in all vertebrae, thereby ignoring the difference in 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 manufacturer and types on the BA measurement, but CT scanners were used in daily clinical practice at all participating centres 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 depending on user-input. In a substudy of 25 subjects, ICC's (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 one year, we have used the BA measurements of baseline and one 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 one year results were compared.

Our study has several strengths. The ECLIPSE study is a large, multicentre study that included both males and females, increasing the generalisability 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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Supplementary material

Additional Supporting Information may be found in the online version of this article. (https://doi.org/10.1007/s00198-019-04977-w)

Supplemental data: Additional information about subject in- and exclusion and vertebral fracture (VF) assessment

Subjects

COPD GOLD classification: stages II to IV according to the Global Initiative for Chronic Obstructive Lung Disease guidelines

	FEV_1	FEV_1/FVC
Stage II	< 80%	< 0.70
Stage III	30% - 50%	< 0.70
Stage IV	< 30%	< 0.70

FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
Both FEV_1 and FVC were expressed in % predicted of someone of the same age, sex, race, and body composition

Subjects with COPD were recruited from the outpatient clinics of the participating centres in Europe, North America, and New Zealand.

Subjects without COPD were recruited through site databases and other methods (advertisements in local newspapers and television/radio stations) where appropriate.

Subjects with significant respiratory disorders or inflammatory diseases other than COPD (such as lung cancer, tuberculosis, or rheumatoid arthritis) or with severe α1-antitrypsin deficiency were excluded from the ECLIPSE study. Also subjects having undergone lung surgery, having cancer or having had cancer in the 5 years prior to enrolment, subjects unable to walk, or subjects who showed evidence of alcohol or drug abuse were excluded.

VF assessment

SpineAnalyzer morphometry software (1-3) detects vertebral shape on lateral images based on user-indicated points. All of the automatically detected points of the six-point morphometry were manually checked and adjusted if necessary.

If VFs were quantitatively identified on the three-year scan, also the one-year scan was quantitatively assessed. If VFs were quantitatively identified on the one-year scan, also the baseline scan was assessed. All images were assessed by one experienced reader, who knew time sequence of the image and that there was at least one VF on the following scan, but who was blinded to patient characteristics and number, location and severity of VFs.

All images with one or more VFs on the three-year scan were additionally assessed by an experienced clinician who was not involved in the primary assessment. In case of any doubt about the nature of the deformity, a second clinician independently assessed the images.

Supplementary Table 4.1 *Baseline characteristics of total ECLIPSE population, and of subjects excluded or included in our study*

	Total ECLIPSE n = 2298		**Excluded*** n = 1059		**Included** n = 1239	
Age (years, mean ± sd)	62.3	7.9	63.4	7.7	61.3	8.0
Sex (M, n (%))	1439	62.6	682	64.4	757	61.1
BMI (kg/m2, mean ± sd)	26.6	5.5	27.5	6.4	25.8	4.5
no COPD (n (%))	327	14.2	87	8.2	240	19.4
COPD GOLD stage I (n (%))	2	0.1	2	0.2	0	
COPD GOLD stage II (n (%))	878	38.2	410	38.7	468	37.8
COPD GOLD stage III (n (%))	829	36.1	409	38.6	420	33.9
COPD GOLD stage IV (n (%))	262	11.4	151	14.3	111	9.0
Smoking status:						
Current smoker (n (%))	916	39.9	392	37.0	524	42.3
Former smoker (n (%))	1382	60.1	667	63.0	715	57.7
Pack years (mean ± sd)	46.2	27.1	49.6	29.1	43.3	24.8

**Due to one or more missing scans, scan quality, etc.*

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease

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Chapter 5

Thoracic Kyphosis on Chest CT Scans Is Associated With Incident Vertebral Fractures in Smokers

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Abstract

Greater kyphosis angles lead to increased loading on vertebral bodies in computational models. However, results about the relationship between severity of kyphosis and incident vertebral fracture (VF) risk have been conflicting. Therefore, the aim of this study was to evaluate associations between *a)* prevalent VFs and severity of kyphosis, and *b)* severity of kyphosis and incident VF risk, in smokers with or without COPD.

Former and current smokers with or without COPD were included. CT scans were made at baseline, one-year and three-year follow-up. VFs were evaluated on superposed sagittal CT reconstructions. Kyphosis was measured as the angle between the lines above T_4 and below T_9 or T_{12}.

We included 1239 subjects (mean age 61.3±8.0, 61.1% male, 80.6% with COPD), of whom 253 (20.4%) had a prevalent VF and 294 (23.7%) an incident VF within three years. Presence, number and severity of prevalent VFs were associated with a greater kyphosis angle. The mean increase in kyphosis angle within three years was small, but significantly greater in subjects with incident VFs compared to those without (2.2±4.1 vs. 1.2±3.9 degrees, respectively, for T_4-T_{12} angle, $p<0.001$).

After adjustment for bone attenuation (BA) and prevalent VFs, baseline kyphosis angle was associated with incident VFs within one and three years (angle T_4-T_{12} per +1SD HR: 1.34 [1.12-1.61] and HR: 1.29 [1.15-1.45], respectively).

Our data showed that a greater kyphosis angle at baseline was independently associated with increased risk of incident VFs within one and three years, supporting the theory that greater kyphosis angle contributes to higher biomechanical loads in the spine.

Introduction

Chronic obstructive pulmonary disease (COPD) is caused by significant exposure to noxious particles and gases, most often tobacco smoking but also exposure to air pollution.[1-4] It is characterized by chronic airflow limitation that is caused by a mixture of small airways disease (e.g. obstructive bronchiolitis) and parenchymal destruction (emphysema). Although COPD is primarily a pulmonary disease, there are significant comorbidities and extrapulmonary effects, such as cardiovascular disease, diabetes, muscle wasting, and osteoporosis. [5-8] The reported prevalence of vertebral fractures (VFs) is high among patients with COPD (9-79%) [9-18] and we have recently shown that incident VF risk is high in COPD patients and (former) smokers without COPD with one or more prevalent VFs.[19]

Hyperkyphosis, an excessive increase in thoracic spinal curvature, is a common condition estimated to affect about 20-40% of the older population.[20] However, since normal kyphosis is increasing with age, cutoff values defining hyperkyphosis are lacking.[21] Although presence of VFs is often reported to be the main cause of increased kyphosis, more than half of the hyperkyphotic patients do not have VFs.[21] Other possible causes can be Scheuermann's disease, intervertebral disk degeneration, and muscle weakness.[21]

Consequences of increased kyphosis are decreased gait performance,[22] increased fall risk tendency[23] and decreased quality of life.[22] Although evidence is limited, it is a common belief that increased thoracic kyphosis limits pulmonary capacity.[24] VFs are associated with increased kyphosis, and additionally, increased kyphosis can contribute to increased fracture risk, even when adjusted for prior fracture history.[25,26]

A computational model showed that during most daily activities, loading is highest in the thoracolumbar and lumbar spine.[27] In addition, increase in thoracic kyphosis was associated with increased loading mainly in the thoracolumbar spine, suggesting that a greater kyphosis angle is related to increased VF risk.[28]

However, clinical data on the relationship between increased kyphosis and incident VF risk have been conflicting. Roux et al. assessed 1624 subjects from the Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment of Peripheral Osteoporosis (TROPOS) studies, and found RRs of 1.30 (1.00-1.68) and 1.42 (1.08-1.86) when the highest T_4-T_{12} angle tertile was compared to the medium and to the lowest tertile respectively, after adjustment for age, BMI, spine bone mineral density (BMD), and prevalent VFs.[29] In contrast, Katzman et al. assessed 3038 women with low BMD from the Fracture Intervention Trial, and did not find a significant influence of increased C_7-T_{12} kyphosis angle on incident VF risk after adjustment for prevalent VFs.[30]

Aim

Since smokers with or without COPD are at increased risk of VFs and chest CT scans are regularly made especially in COPD patients, it would be interesting to know whether thoracic kyphosis as measured on CT is an independent risk factor for incident VFs. Therefore, our aim was to evaluate the associations between *a)* prevalent VFs and thoracic kyphosis angle, and *b)* between thoracic kyphosis angle and incident VFs, in current and former smokers with or without COPD.

Materials and Methods

Subjects

Current and former smokers with or without COPD from the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; Clinicaltrials.gov identifier NCT00292552; GlaxoSmithKline study SCO104960) were included. The ECLIPSE study is a non-interventional, observational, multicenter study that was started to search underlying mechanisms of disease progression in subjects with COPD and to identify biomarkers that may serve as surrogate endpoints and therefore could measure disease progression. Detailed inclusion and exclusion criteria were described elsewhere.[31,32] In short, subjects aged 40-75, with a smoking history of at least 10 pack years (1 pack year = 20 cigarettes (1 pack) per day for one year), either with moderate to very severe COPD (stage II-IV (stage II: 50%≤FEV_1<80% predicted (FEV_1: forced expiratory volume in 1 second), and FEV_1/FVC <0.70 (FVC: forced vital capacity); stage III: 30% ≤ FEV_1 <50% predicted, FEV_1/FVC <0.70; stage IV: FEV_1 < 30% predicted, FEV_1/FVC < 0.70) according to the GOLD guidelines, Global Initiative for Chronic Obstructive Lung Disease) or without COPD (FEV_1 >85% predicted, FEV_1/FVC >70%) were included. Both current and former smokers were eligible. Subjects with respiratory diseases other than COPD were excluded, as well as subjects with an exacerbation requiring treatment in the four weeks prior to enrollment, and subjects using oral glucocorticosteroids (GC) at baseline. Only subjects with complete set of CT scans at baseline, one-year and three-year follow up were included; subjects with scans of insufficient quality, or lack of clear anatomic landmarks to identify vertebrae were not eligible for this study.[19]

Measurements

Demographic and pulmonary parameters were collected at baseline, one-year and three-year follow-up. Also pack years and smoking status (current or former) were evaluated. Detailed information can be found elsewhere.[31,32]

CT scan analyses and VF assessment

At baseline, one-year and three-year follow-up, CT scans of the chest were performed at full inspiration (120 kV peak, 40 mAs, 1.00 or 1.25-mm volumetric acquisition, General Electric (GE) or Siemens). Of all sagittal reformats containing the spine, the contrast was adjusted to (partly) eliminate soft tissue. Subsequently, all sagittal reformats containing the spine were superposed to create simulated lateral X-ray 2D images using Matlab (version R2013a, MathWorks®, Natick, MA, USA). Images were exported in DICOM-format.[19,33]

VF assessment was described in detail elsewhere.[19] In short, vertebrae were first visually evaluated and were, after exclusion of deformities due to Scheuermann's disease, Schmorl's noduli, or platyspondyly, marked as 'VF' or 'no VF'. Next, in case of positive evaluation, vertebrae were morphometrically assessed using SpineAnalyzer software (Optasia Medical, Cheadle, UK).[33-35] Based on the amount and location of height loss as measured by the software, VFs were classified according to the scoring method proposed by Genant et al. as grade 1 (mild: 20-25% height reduction in vertebral body), grade 2 (moderate: 25-40%), or grade 3 (severe: >40% height loss in vertebral body).[36] In addition, severity and number of VFs from T_4 to L_1 was expressed as the spinal deformity index (SDI),[37] which is calculated as the sum of the grades of all VFs within the subject (e.g. a subjects with two grade 2 VFs and one grade 3 VF has an SDI of 7).

If one or more VFs (any shape or grade) were quantitatively assessed on the three-year scan, also the one-year scan was quantitatively assessed. If VFs were quantitatively assessed on the one-year scan, also the baseline scan was assessed. Incident VFs were defined as new VFs (from no VF to any grade of VF) or worsening VFs (e.g. from a grade 2 to a grade 3 VF) between baseline and one-year follow-up, and between baseline and three-year follow-up.

According to Genant et al., a VF can be wedge shaped (anterior height loss), biconcave shaped (middle height loss), or crush shaped (height loss of total vertebral body). SpineAnalyzer morphometry software uses the following guidelines to classify shapes of the VFs:

$$Deformity\ wedge\ \% = 100 * (\ 1 - {}^{h_A}/_{h_P}\ )$$

$$Deformity\ biconcave\ \% = 100 * (\ 1 - {}^{h_M}/_{h_P}\ )$$

$$Deformity\ crush\ \% = 100 * (\ 1 - \min\ (\max\ ({}^{h_{Pi}}/_{h_{Pi-1}}, {}^{h_{Ai}}/_{h_{Ai-1}}), \max\ ({}^{h_{Pi}}/_{h_{Pi+1}}, {}^{h_{Ai}}/_{h_{Ai+1}}))$$

- h_A = *anterior height of vertebral body*
- h_P = *posterior height of vertebral body*
- h_M = *mid height of vertebral body*
- i = *level of vertebra measured*
- i *+1 or I -1 = vertebral level above resp. below the measured vertebra*

If both posterior and mid height of the vertebral body showed height loss (for example a VF with 41% mid height loss, and 24% anterior height loss), SpineAnalyzer indicated both VF shapes (biconcave and wedge). In such cases, VFs were scored according to the largest deformation.

Bone attenuation

Bone attenuation (BA) was measured on CT in vertebrae T_4 to T_{12}, using a self-written algorithm in Matlab (R2013a, MathWorks, Natick, MA, USA). BA was measured semi-automatically in cubic areas of approximately 275mm^3 each (slightly varying due to voxel size). Vertebrae that were diagnosed with a VF, or that showed other abnormalities such as Scheuermann's disease, Schmorl's noduli, or platyspondyly (in concertation of MvD, PG, and JvdB) were excluded from BA measurement. BA was measured as the mean of T_4 to T_{12} and expressed in Hounsfield Units (HU).

Kyphosis

To measure kyphosis angles, a 3rd order polynomial was fit through the spine based on user-indicated points centered in the intervertebral disks (see Figure 5.1, self-written algorithm in Matlab). The 3rd order polynomial was fitted in the sagittal (2D) plane, therefore curvature in the coronal plane did not influence the polynomial. Large curvature in the coronal plane, such as observed in scoliotic patients, resulted in unclear images of the vertebrae on the simulated X-ray images, and therefore these patients were not included in this study. Kyphosis was

measured as the angle between two lines perpendicular to the polynomial, crossing the polynomial closest to the user-indicated points in the intervertebral disks. The angles between T_4 and T_9 (lines crossing polynomial in the intervertebral disks above T_4 and below T_9) and between T_4 and T_{12} (lines crossing above T_4 and below T_{12}) were measured (Figure 5.1). The mean r^2 for the degree of fit of the polynomial to the user-indicated points was 0.99 (range 0.9323-0.9998), and the ICC (intraclass correlation coefficient) of triple measurements of a subset of n=25 scans was excellent (ICC>0.95, data not published). In addition, kyphosis angles measured using this method were compared to kyphosis angles between vertebral endplates measured using Surgimap software (Surgimap®, Nemaris Inc.™, New York, USA; available via www.surgimap.com), and showed very good correlations (n=92 and n=77 for T_4-T_9 and T_4-T_{12} angles, respectively; r^2>0.85, data not published) for both the T_4-T_9 and the T_4-T_{12} angle.

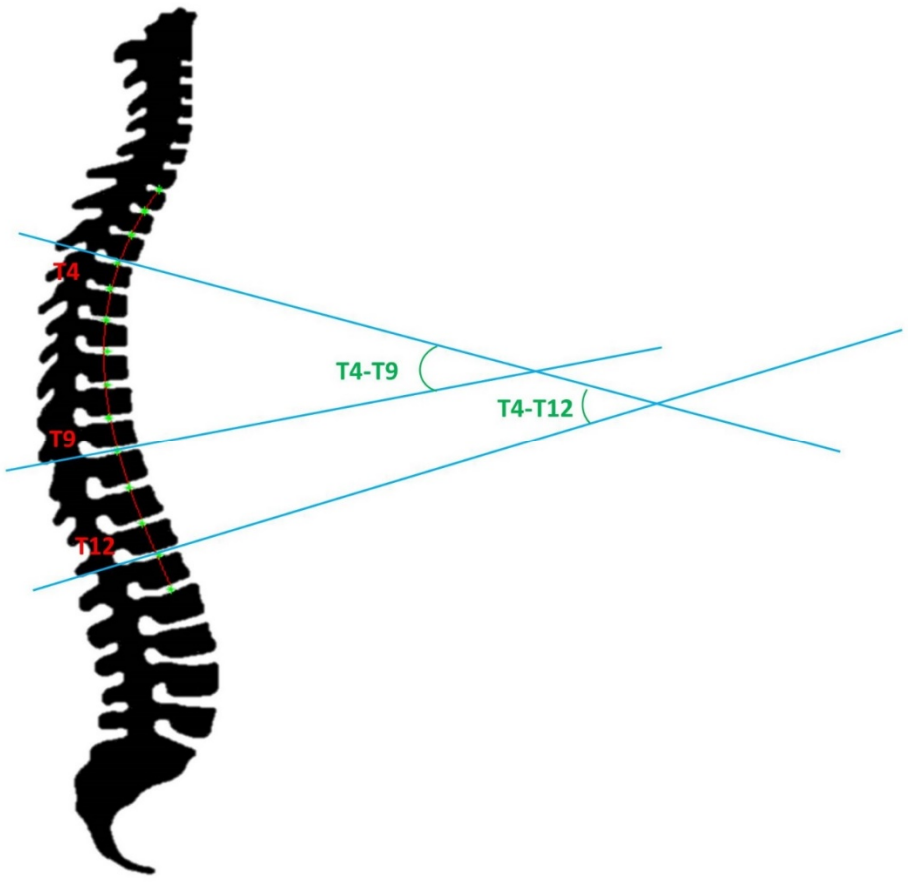

Figure 5.1 *Measurement of kyphosis angles (T_4-T_9 and T_4-T_{12}) by 3rd order polynomial*
User-indicated points (green) were placed centered in the intervertebral disks, and a 3rd order polynomial (red) was fit through these points. The angle between T_4 and T_9 was measured as the angle between two lines (blue), above T_4 and below T_9, perpendicular to the 3rd order polynomial closest to the user-indicated points above T_4 and below T_9, respectively. The lines above T_4 and below T_{12} were used to measure the angle between vertebrae T_4 and T_{12}.

Outcome measures and statistics

Main outcome measures were baseline kyphosis angles, change in kyphosis angles, and incidence of VFs.

Possible confounders were age, sex, presence of COPD, BMI, pack years, smoking status (current or former), BA, and prevalent VFs. Age, sex, and presence of COPD were included in all models; other confounders were included if they influenced the beta-coefficient of the main exposure more than 5%, or when consensus consisted within the team of researchers supported by evidence from literature.

To evaluate associations between prevalent VFs and kyphosis angle, and between incident VFs and change in kyphosis angle, linear regression models were used (SAS 9.3, SAS Institute, Cary, NC, USA; REG procedure).

Because the prevalence of the outcome measure 'incident VFs' is 10% over a one-year time period and 24% over the three-year time period, Cox proportional hazard models (PHREG procedure) were used to evaluate the associate between baseline kyphosis and incident VFs. Hazard ratios (HR's) are given with 95% confidence interval [95%CI], and are given per standard deviation for continuous variables.

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-up). Of these, 237 subjects were excluded due to various reasons (scan quality (noise, missing slices, incorrect slice spacing; n=156); anatomy (could not identify T1/vertebral levels, deformation of the spine; n=14); failure of the method to edit CT scans (slice numbers not in ascending order and/or not starting at 0 or 1, problems with white balance in Matlab, or unclear adapted CT images; n=60); or use of oral GC at baseline (n=7)). Additionally, two subjects were excluded due to multiple deformations other than VFs (platyspondyly, Scheuermann's disease; for flowchart and characteristics of in- and excluded subjects, see elsewhere [19]). Thus, 1239 subjects were included (999 subjects with and 240 subjects without COPD). Baseline characteristics are given in Table 5.1. There were 133 (11%) subjects using inhaled steroids at baseline, 123 (10%) at one-year and 116 (9%) at three-year follow-up. There were 23 (2%) subjects using oral steroids at the time of one-year follow-up, and 47 (4%) at three-year.

Table 5.1 *Baseline characteristics*

	Included subjects n = 1239		**Men** n = 757		**Women** n = 482	
Age (years: mean, sd)	61.3	8.0	62.2	8.0	60.0	7.8
Sex (male: n, %)	757	61.1				
BMI (kg/m^2: mean, sd)	25.8	4.5	26.1	4.4	25.2	4.7
With COPD (n, %)	999	80.6	618	81.6	381	79.0
Current smoker (n, %)	524	42.3	305	40.3	219	45.4
Pack years (mean, sd)	43.3	24.8	46.9	26.7	37.6	20.4
≥1 prevalent VF (n, %)	253	20.4	185	24.4	68	14.1
≥2 prevalent VF (n, %)	113	9.1	84	11.1	29	6.0
Grade 2 or 3 prevalent VF (n, %)	132	10.7	91	12.0	41	8.5
Kyphosis T_4-T_9 (degrees: mean, sd)	26.4	7.7	25.8	7.8	27.5	7.6
Kyphosis T_4-T_{12} (degrees: mean, sd)	34.5	10.2	33.4	10.3	36.2	9.7
Incident VFs one year (n, %)	117	9.4	86	11.4	31	6.4
Incident VFs three years (n, %)	294	23.7	205	27.1	89	18.5

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; VF = vertebral fracture

1 pack year = 20 cigarettes per day for one year

Table 5.2 *Number and shape of prevalent vertebral fractures per vertebral level*

	Vertebrae and VFs			**VF by any deformation (overlapping)**						**VF by highest deformation (mutually exclusive)**					
	Total no. scored	**With VF**		**With (also) wedge shape**		**With (also) biconcave shape**		**With (also) crush shape**		**Wedge as highest deformation**		**Biconcave as highest deformation**		**Crush as highest deformation**	
	n	n	%	n	% (of VF)	n	% (of VF)	n	% (of VF)	n	% (of VF)	n	% (of VF)	n	% (of VF)
T_4	1236	14	1.1	7	50.0	11	78.6	2	14.3	3	21.4	10	71.4	1	7.1
T_5	1233	24	1.9	19	79.2	16	66.7	4	16.7	14	58.3	8	33.3	2	8.3
T_6	1227	38	3.1	34	89.5	18	47.4	1	2.6	29	76.3	9	23.7	0	0.0
T_7	1232	74	6.0	72	97.3	26	35.1	1	1.4	65	87.8	9	12.2	0	0.0
T_8	1235	85	6.9	81	95.3	26	30.6	2	2.4	74	87.1	11	12.9	0	0.0
T_9	1236	43	3.5	36	83.7	21	48.8	4	9.3	28	65.1	13	30.2	2	4.7
T_{10}	1236	13	1.1	12	92.3	6	46.2	0	0	9	69.2	4	30.8	0	0.0
T_{11}	1231	50	4.1	43	86.0	21	42.0	2	4.0	39	78.0	10	20.0	1	2.0
T_{12}	1198	67	5.6	59	88.1	27	40.3	3	4.5	49	73.1	18	26.9	0	0
L_1	999	30	3.0	27	90.0	15	50.0	1	3.3	21	70.0	9	30.0	0	0
TOTAL	12063	438	3.6	390	89.0	187	42.7	20	4.6	331	75.6	101	23.1	6	1.4

Abbreviations: VF = vertebral fracture

Due to VF definitions by SpineAnalyzer morphometry software, VFs can have multiple configurations. In the section 'VF by any deformation (overlapping)' any shape of VF was scored, and therefore VF shapes can overlap (for example: a vertebra with 41% biconcave and 24% wedge has two VF shapes). In the section 'VF by highest deformation (mutually exclusive)' VFs were scored according to the highest deformation in percentage. These three columns are mutually exclusive.

Table 5.3 *Change in kyphosis angles within one and three year in subjects with or without incident vertebral fractures*

	ONE YEAR INCIDENCE						**THREE YEAR INCIDENCE**					
	Without incident VF n=1117		**With incident VF n=117**		**p-value**		**Without incident VF n=943**		**With incident VF n=294**		**p-value**	
	mean	sd	mean	sd	*	**	mean	sd	mean	sd	*	**
Kyphosis T_4-T_9	25.9	7.4	31.1	9.3	<.0001		25.4	7.1	29.7	8.9	<.0001	
Kyphosis T_4-T_{12}	33.8	9.8	40.7	10.8	<.0001		32.9	9.5	39.6	10.6	<.0001	
ΔT_4-T_9 within one year	0.3	2.5	0.8	2.9	0.0277	0.0040						
ΔT_4-T_{12} within one year	0.2	3.6	1.3	4.2	0.0045	0.0000						
ΔT_4-T_9 within three year							1.0	2.7	1.7	3.2	0.0003	0.0004
ΔT_4-T_{12} within three year							1.2	3.9	2.2	4.1	0.0002	<.0001

**adjusted for age and sex*

*** adjusted for age, sex, and kyphosis at baseline*

Abbreviations: VF = vertebral fracture. All kyphosis angles and change in kyphosis angles are given in degrees.

Of all vertebrae that were evaluated (n=12063), 438 (3.6%) showed a VF grade 1 or higher at baseline (Table 5.2). Most VFs (63.0%) were located in the mid-thoracic (T_7-T_8) and thoracolumbar area (T_{11}-T_{12}, see Supplementary Figure 5.1, online supplement).

Of all VFs, most VFs were wedge shaped (75.6%). An even larger proportion of VFs had height loss at the anterior side of the vertebral body (89.0%) but did not necessarily have wedge shape as largest deformation.

The mean kyphosis angle of subjects with one or more prevalent VF (n=248) was 30.1 ±9.3 degrees for angle T_4-T_9, and 40.5 ±10.6 for angle T_4-T_{12}. Both kyphosis angles were significantly greater compared to subjects without prevalent VFs (n=989, 25.5 ±7.0 degrees for angle T_4-T_9, and 33.0 ±9.4 for angle T_4-T_{12}, respectively).

After adjustment for age and sex, the mean kyphosis angle was significantly greater in subjects with multiple VFs (n=108 with ≥2 VFs, mean T_4-T_9 angle: 33.3 ±10.0; mean T_4-T_{12} angle: 43.7 ±11.3) compared to subjects with only 1 VF ($p<0.001$ for both angles) or without VFs ($p<0.001$ for both angles). Also in subjects with severe VFs (n=33 with at least 1 grade 3 VF, mean T_4-T_9 angle: 36.2 ±10.9; mean T_4-T_{12} angle: 46.1 ±10.6) mean kyphosis angle was significantly greater compared to subjects with a grade 2 VF ($p<0.001$ for T_4-T_9 angle; $p=0.003$ for T_4-T_{12} angle), subjects with a grade 1 VF ($p<0.001$ for T_4-T_9 angle; $p=0.006$ for T_4-T_{12} angle), or subjects without VFs ($p<0.001$ for both angles). The same applied to subjects with an SDI of ≥5 (n=36, mean T_4-T_9 angle: 37.1 ±11.5; mean T_4-T_{12} angle: 48.2 ±12.6) compared to subjects with an SDI of 3-4 ($p=0.002$ for T_4-T_9 angle; $p=0.004$ for T_4-T_{12} angle), with an SDI of 1-2 ($p<0.001$ for both angles), or subjects without VFs ($p<0.001$ for both angles).

In line with prevalent VFs, most incident VFs occurred in T_7-T_8 and T_{11}-T_{12} (56% and 58% for one-year and three-year incidence). For the one-year incidence, also T_6 (13%) was a frequent location for incident VFs.

The mean increase of the kyphosis angle in the total population within one (ΔT_4-T_9: 0.3 ±2.6; ΔT_4-T_{12}: 0.3 ±3.7) and within three years (ΔT_4-T_9: 1.2 ±2.8; ΔT_4-T_{12}: 1.4 ±4.0) was small. The mean increase was larger in subjects with incident VFs compared to subjects without incident VFs (Table 5.3).

Table 5.4 *Univariate and multivariate associations between baseline kyphosis angle and risk of incident vertebral fractures within one and three years*

	Univariate		**Multivariate with T_4-T_9**		**Multivariate with T_4-T_{12}**	
ONE YEAR INCIDENCE	HR	95%CI	HR	95%CI	HR	95%CI
Age (per +8 years)	1.42	[1.167-1.738]	0.99	[0.789-1.251]	0.97	[0.771-1.225]
Sex (M vs F)	1.78	[1.179-2.679]	1.65	[1.082-2.525]	1.83	[1.182-2.841]
BMI (per +5 kg/m^2)	0.85	[0.696-1.049]	-		-	
Pack years (per +25 pack years)	1.06	[0.895-1.264]	-		-	
Smoking status (Current vs Former smoker)	0.79	[0.542-1.150]	-		-	
with COPD (vs. no COPD)	1.64	[0.955-2.823]	0.88	[0.492-1.587]	0.83	[0.444-1.538]
GOLD stage II (vs. no COPD)	1.45	[0.803-2.611]	-		-	
GOLD stage III (vs. no COPD)	1.57	[0.867-2.828]	-		-	
GOLD stage IV (vs. no COPD)	2.74	[1.392-5.390]	-		-	
≥1 prevalent VF (vs. no VF)	5.41	[3.749-7.799]	3.30	[2.181-4.987]	3.20	[2.096-4.898]
BA (per -47 HU)	2.00	[1.618-2.475]	1.39	[1.104-1.761]	1.46	[1.147-1.856]
Kyphosis T_4-T_9 (per +8 degrees)	1.70	[1.453-1.978]	1.31	[1.113-1.533]	-	
Kyphosis T_4-T_{12} (per +10 degrees)	1.76	[1.489-2.076]	-		1.34	[1.121-1.608]
THREE YEAR INCIDENCE						
Age (per +8 years)	1.30	[1.154-1.473]	1.03	[0.892-1.184]	1.01	[0.872-1.162]
Sex (M vs F)	1.47	[1.147-1.886]	1.33	[1.029-1.717]	1.41	[1.082-1.828]
BMI (per +5 kg/m^2)	0.93	[0.815-1.053]	-		-	
Pack years (per +25 pack years)	1.10	[0.990-1.222]	-		-	
Smoking status (Current vs Former smoker)	0.93	[0.736-1.172]	-		-	
with COPD (vs. no COPD)	1.30	[0.947-1.777]	1.03	[0.729-1.445]	1.00	[0.699-1.433]
GOLD stage II (vs. no COPD)	1.22	[0.863-1.719]	-		-	
GOLD stage III (vs. no COPD)	1.32	[0.934-1.865]	-		-	
GOLD stage IV (vs. no COPD)	1.55	[0.992-2.426]	-		-	
≥1 prevalent VF (vs. no VF)	3.88	[3.087-4.873]	2.82	[2.178-3.644]	2.62	[2.006-3.413]
BA (per -47 HU)	1.60	[1.410-1.822]	1.23	[1.068-1.413]	1.26	[1.086-1.450]
Kyphosis T_4-T_9 (per +8 degrees)	1.47	[1.324-1.628]	1.21	[1.068-1.344]	-	
Kyphosis T_4-T_{12} (per +10 degrees)	1.58	[1.420-1.757]	-		1.29	[1.147-1.448]

Abbreviations: VF = vertebral fracture; HR = Hazard Ratio; CI = confidence interval BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease

For continuous variables, HR's are given per standard deviation.

In subjects with an increase in SDI of >2 within three years, the increase in kyphosis angle (n=77, ΔT_4-T_9 angle: 3.0 ±3.8 and ΔT_4-T_{12} angle: 4.4 ±4.3) was significantly higher than in subjects without incident VFs, with an increase in SDI of 1, or 2 ($p<0.01$ for both angles). The increase in kyphosis in subjects with an increase in SDI of >2 within one year (n=10) was not significantly different from the other groups.

In univariate models, both T_4-T_9 and T_4-T_{12} kyphosis angles at baseline were significantly associated with incident VFs within one and within three years (Table 5.4). In multivariate models, the baseline kyphosis angle remained a significant determinant of incident VFs. However, a prevalent VF was a much stronger determinant.

Discussion

In this study, we showed that prevalent VFs are associated with greater kyphosis angles, and that greater kyphosis angles at baseline are independently associated with incident VFs, within one and three years. Although a prevalent VF is a stronger determinant, both baseline BA and kyphosis angle contribute to incident VF risk. Out data support the theory that greater kyphosis angle contributes to higher biomechanical loads in the spine and hence may lead to increased VF risk.

In line with literature,[38-40] we found that both prevalent and incident VFs were observed most frequently in T_7-T_8 and T_{11}-T_{12}. A computational model of the spine showed that during daily activities vertebral compressive load was highest in the thoracolumbar (T_{11}-L_1) and lumbar spine (L_2-L_5). Due to the higher vertebral strength in the lumbar spine, the risk of VFs was highest in the thoracolumbar area and in vertebra T_6 during some activities.[27] These findings could explain the high prevalence and incidence of VFs in the thoracolumbar area.

Similar to previous results,[37] we found significant associations between prevalent VFs and baseline kyphosis angle, and between incident VFs and increase in kyphosis angle after one- and three-year follow-up.

Our data also showed that a greater baseline kyphosis angle was an independent determinant for incident VFs. Bruno et al. showed in a computational model that with greater kyphosis angles, the load within the spine was higher during daily activities than in less kyphotic spinal models.[28] In line with our data Roux et al. also found an independent association between kyphosis angle and incident VFs,[29] but Katzman et al. did not.[30] Different methods of kyphosis measurement, imaging methods, and positioning of patients were used (measured on left lateral decubitus position X-ray (T_4-T_{12} angle); Debrunner kyphometer in standing position (C_7-T_{12} angle)) while we used CT scans taken in supine position. In addition, patient populations were slightly different (both studies included women only, selected based on prevalence of VFs, or based on T-score, and the population in the study by Roux et al. was older).

The associations we found support the hypothesis that the load-to-bone strength ratio is highest in the thoracolumbar area and during some activities in the high/midthoracic area, and that the biomechanical effect of greater kyphosis angle could contribute to a higher load-to-bone strength ratio.

This study has some limitations.

First, there is selection bias; only former and current smokers of non-Hispanic white ethnicity with or without COPD were included. Subjects were recruited from outpatient clinics with GOLD II, GOLD III, or GOLD IV (with COPD) or through site databases and advertisement (without COPD). Subjects using oral GC at baseline were excluded, and there was no information available about history of steroid use or use of medications such as bisphosphonates. We excluded subjects with incomplete set of CT scans of insufficient quality. In addition, only a limited number of GOLD IV subjects (n=111) and subjects without COPD (n=240) were included. These in- and exclusion criteria limit the applicability to the general COPD and/or (former) smoker population.

Second, kyphosis angles were measured on chest CT images taken in supine position. It is expected that in standing position, gravitational forces influence thoracic kyphosis to a higher extend than in supine position, leading to an underestimation of the measured kyphosis angle in our study. However, studies comparing kyphosis angles in supine and in standing position showed that these measures are well associated.[41,42] Therefore, supine images could serve as alternative to standing recordings for kyphosis measurement.

In addition, only the thoracic spine and first lumbar vertebrae were imaged on chest CT, and therefore prevalent and incident VFs in the lumbar spine, as well as lordosis angles could not be measured.

Furthermore, kyphosis angles were measured for this research using a new method, via a 3rd order polynomial fit through user-indicated points in the spine. Using this method, the measured angles describe the curvature of the spine rather than the influence of individual endplate deviations. The method is depending on user-input, but precision in repeated measures, as well as correlations with another angle measurement method were very good.

Lastly, BA is not a standardized method of bone density measurement. However, there are several papers showing the associations between BA by CT and BMD by DXA, or between BA by CT and vertebral fractures.[43]

In this study we found an association between prevalent VFs and CT-measured baseline kyphosis angle, and between incident VFs and increase in kyphosis angle. In addition, baseline kyphosis angle was associated with short-term VF incidence after adjustment for BA and prevalent VFs. These results support the theory that greater kyphosis angles contribute to higher biomechanical loads in the spine and may attribute to short term VF risk.

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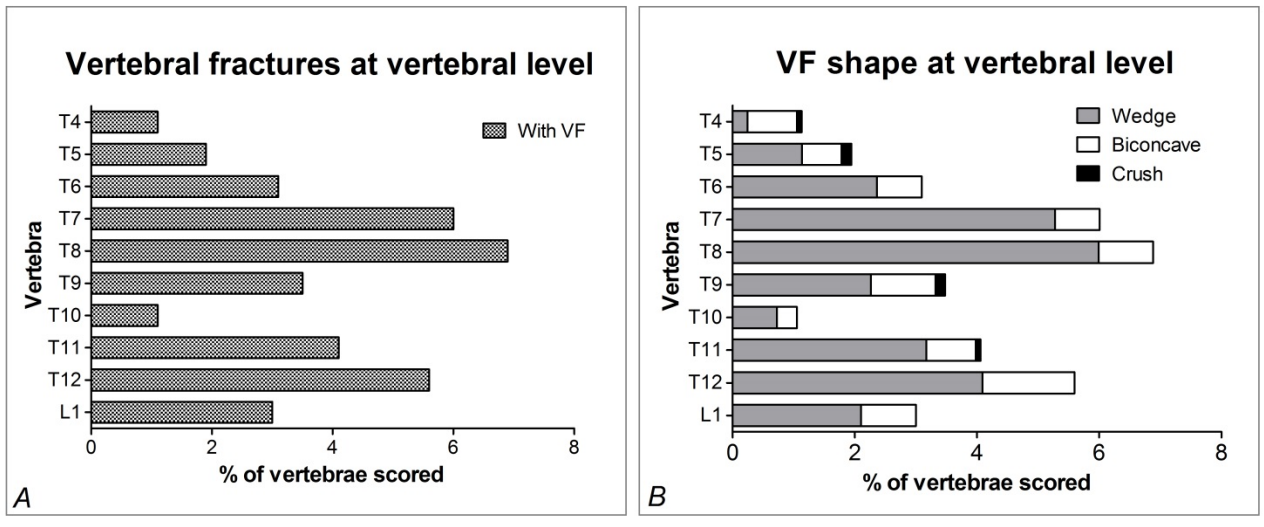
Supplementary material



Supplementary Figure 5.1 *Number and shape of prevalent vertebral fractures*

A*) Percentage of vertebrae with vertebral fractures (VFs) of any shape, and* ***B****) Shapes of vertebral fractures*

VFs are expressed in % of the vertebrae that were scored at that specific vertebral level. The number of vertebrae scored at each level can be found in Table 5.2.

Chapter 6

Associations between bone attenuation and prevalent vertebral fractures on chest CT scans differ with vertebral fracture locations

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Abstract

Purpose - Vertebral fractures (VFs) are associated with low bone mineral density but are not equally distributed throughout the spine and occur most commonly at T7-T8 and T11-T12 ("cVFs") and less commonly at T_4-T_6 and T_9-T_{10} ("lcVF"). We aimed to determine whether associations between bone attenuation (BA) and VFs vary between subjects with cVFs only, with lcVFs only, and with both cVFs and lcVFs.

Methods - Chest CT images of T_4-T_{12} in 1237 smokers with and without COPD were analysed for prevalent VFs according to the method described by Genant (11133 vertebrae). BA (expressed in Hounsfield units) was measured in all non-fractured vertebrae (available for 10489 vertebrae).

Linear regression was used to compare mean BA and logistic regression was used to estimate the association of BA with prevalent VFs (adjusted for age and sex).

Results - On vertebral level the proportion of cVFs was significantly higher than of lcVF (5.6% vs 2.0%).

Compared to subjects without VFs, BA was 15% lower in subjects with cVFs ($p<0.0001$), 25% lower in subjects with lcVFs ($p<0.0001$) and lowest in subjects with cVFs and lcVFs (-32%, $p<0.0001$).

The highest ORs for presence of VFs per -1SD BA per vertebra were found in subjects with both cVFs and lcVFs (3.8 to 4.6).

Conclusions - The association between VFs and BA differed according to VF location. ORs increased from subjects with cVFs, to subjects with lcVFs and were highest in subjects with cVFs and lcVFs, indicating that other factors than only BA play a role in the bimodal VF distribution.

Introduction

Vertebral fractures (VFs) are the most common fractures in the population older than 50 years.[1] Subjects with prevalent VFs have lower bone mineral density (BMD) in the lumbar spine and hip than subjects without VFs,[2] and low BMD in the lumbar spine and femoral neck is a risk factor for incident VFs.[3]

However, the prevalence of VFs is not equally distributed across the spine[4] and in the thoracic spine it is highest at T_7-T_8 and T_{11}-T_{12}.[5-7] The reasons for this bimodal distribution of VFs remain unclear. Two hypotheses have been explored in this context, one exploring the association between BMD and the location of VFs, and one exploring the association between vertebral loading and the location of VFs.

In several studies the associations between BMD and the presence or incidence of VFs were evaluated according to their locations. In a community-based study, prevalent VFs in the upper spine were more strongly associated with BMD (measured by QCT in T_{10} and L_3) than VFs in the lower spine.[8] In the fracture intervention trial, each SD decrease in the lumbar spine was associated with 2.1 times greater odds of new VFs in the upper spine (T_4-T_{10}) compared with 1.5 times for lower spine VFs (T_{11}-L_4) with a statistical difference between the two ratios.[7] In the VERO trial, patients with only prevalent VFs in other spine regions than T_{12} and L_1 had significantly lower BMD (measured by DXA in the spine, the femoral neck and total hip) than patients with only T12 and/or L1 VFs [9]. The authors of these studies concluded that VFs in the upper spine are more related to bone fragility than VFs in the lower spine and that other factors than BMD play a role in the unequal distribution of VFs in the spine.[7-9]

A study on the biomechanical loading of vertebrae showed that the thoracic regions with the highest prevalence of VFs (T_7-T_8 and T_{11}-T_{12}) are also the thoracic regions that are at highest compression load during daily activities such as bending and lifting objects.[10-13] A study on the epidemiology of traumatic vertebral fractures indicated that the vertebrae T_{11}-T_{12} are at highest risk for fracture when falling.[14] These findings provided a biomechanical mechanism for the higher incidence of fractures in these regions compared to other spinal regions.[10,13]

None of the above-mentioned studies evaluated the association between BMD and VF location separately in subjects with VFs at the most common levels and subjects with VFs at the less common vertebral levels.

Previously taken clinical computed tomography (CT) scans of the chest performed in the context of lung diseases can be used for opportunistic screening for the presence of VFs and to measure BMD in the vertebrae by bone attenuation.[15-18] For this study we used the chest CT scans of the ECLIPSE study, a large cohort of current and former smokers with and without COPD.[19]

Aims

The purpose of this study was to determine whether associations between bone attenuation (BA) and prevalent VFs vary between subjects with VFs at more common locations T_7-T_8 and T_{11}-T_{12} (cVFs) versus less common locations (lcVFs).

We hypothesized that BA is higher in subjects with cVFs than in subjects with lcVFs, because other factors such as a sudden load during a fall or more strenuous daily activities might contribute to a higher extent in VFs at common locations.

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.[19-21] Current or former smokers (40-75 years old) with moderate to very severe COPD (stage II-IV according to the Global Initiative for Chronic Obstructive Lung Disease guidelines[22]), or without COPD, with a smoking history of at least 10 pack years were included.

Measurements

Chest CT scans

CT scans of the chest were performed at full inspiration (120 kV peak, 40 mAs, 1.00 or 1.25 mm volumetric acquisition, General Electric [GE] or Siemens), as described earlier.[17] CT scanners were calibrated regularly using industry and institutional standards.

Of all sagittal reformats containing the spine, the contrast was adjusted to (partly) eliminate soft tissue. Subsequently, all sagittal reformats containing the spine were superposed to create simulated lateral X-ray 2D images using Matlab (version R2013a, MathWorks, Natick, MA, USA). Images were exported in DICOM-format.

Vertebral fracture assessment

Detailed information has been reported elsewhere[23]. Briefly, VFs in vertebrae T_4-T_{12} were first semi quantitatively assessed, where vertebrae were graded as deformed or not deformed. Vertebrae with deformations due to qualitative features of morphology such as Schmorl's nodes, Scheuermann's disease, platyspondyly, or fusion of vertebrae were excluded. In case of height loss in the vertebral body at the anterior side, in the middle, or in the total vertebral

body without other deformities, vertebrae were subsequently morphometrically assessed using the SpineAnalyzer software (Optasia Medical, Cheadle, UK[18,24,25]). VF severity was classified according to the method described by Genant et al. (grade 1: 20-25% height reduction; grade 2: 25-40%; grade 3: >40%).[26]

Subjects were classified according to the presence and location of their VFs. Four subgroups were created: subjects with no prevalent VFs, subjects with VFs only at common locations (cVFs: T_7-T_8, T_{11}-T_{12}), subjects with VFs only at less common locations (lcVFs: T_4-T_6, T_9-T_{10}) and subjects with VFs at both common and less common locations combined.

Bone attenuation

In a previous study, Romme et al. showed that BA measurements on CT correlated well with BMD measurements on DXA in a COPD population (r=0.827, p<0.001).[27] BA was measured on CT in vertebrae T_4 to T_{12}, using a self-written algorithm in Matlab (R2013a, MathWorks, Natick, MA, USA). In a substudy of 25 subjects, ICC's of triple measurements of the same image acquisition showed excellent agreement (ICC=0.998 [0.996-0.999]; single measures, two-way random, absolute agreement, data not published). Fractured vertebrae were excluded from BA measurements, because their BMD is increased following fracture healing due to callus formation. BA was measured as the mean of T_4 to T_{12} and expressed in Hounsfield Units (HU). Analyses were performed using the mean BA of all non-fractured vertebrae ("total BA"). Because there is a gradual decreases in BMD from T_4 to L_3, with Pearson's correlations of >0.90 between thoracic and lumbar vertebrae,[28] we also used the mean BA per vertebra ("local BA"). More details about subjects, image processing, VF assessment and BA measurement have been published elsewhere.[29]

Statistics

Baseline characteristics were compared between the different fracture groups using ANOVA for continuous variables and chi-square test for categorical data. The proportion of VFs at common locations versus less common locations was compared with a McNemar's test for dependent proportions.

Linear regression (proc reg) was used to compare total spine BA and BA per vertebra between the different groups (no VF, only cVF, only lcVF and both cVF and lcVF). The measured BA was the dependent variable, and the different fracture groups were used as independent variables as well as age and sex. Logistic regression (proc logistic) was used to estimate the OR per 50 HU (approximately 1 SD) lower BA and the risk of any VF, a cVF, a lcVF and both cVFs and lcVFs. For this analysis, the event of interest (any VF, a cVF, a lcVF or both cVFs and lcVFs) was the

dependent variable and BA/50 was the independent variable. Age and sex were also added as independent variables.

Based on loads on the vertebrae from the manuscript by Bruno et al.,[10] the load/BA ratio (also referred as "phi"; the ratio of the applied impact force to the bone strength[30]) was indirectly calculated.

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Figures were created using Microsoft Excel 2010.

Results

Baseline characteristics of the 1237 subjects are given in Table 6.1. Mean age of subjects was 61 years, 61% were men, 81% had COPD, 42% were current smokers and 58% were former smokers. Presence of VFs could be measured in 11055 vertebrae and BA was available for 10489 non-fractured vertebrae.

Prevalent VFs were most frequent in T_7-T_8 (>6% of vertebrae) and T_{11}-T_{12} (>4% of vertebrae) (Figure 6.1A). Similar bimodal patterns were found for prevalent grade 1, 2 and 3 VFs separately (Figure 6.1B). The proportion of VFs at common locations was 5.6% compared to 2.0% at the less common locations ($p<0.0001$).

Of the 1237 subjects, 239 (19%) had at least one VF, 197 (16%) had at least one cVF, 100 (8%) at least one lcVFs, 139 (11%) had only cVFs, 42 (3%) had only lcVFs and 58 (5%) had both.

Total BA in subjects according to VF locations

Compared to subjects without a VF and adjusted for age and sex, total BA was 21% lower in subjects with a prevalent VF (128 ±43 versus 162 ±46 HU, mean difference 34HU, $p<0.0001$).

Total BA was 138 ±44 HU in subjects with only cVFs (mean difference without VFs: 23 HU), 122 ±35 HU in subjects with only lcVFS ($p<0.0001$ versus cVFs, mean difference without VFs: 40 HU), and 110 ±36 HU in subjects with a combination of cVFs and lcVFs ($p<0.0001$ vs cVFs, mean difference without VFs: 52 HU) (Figure 6.2). After adjustment for age and sex, all these total BA values were significantly ($p<0.0001$) lower compared to subjects without a VF. The gradual trend in decrease in total BA between no VFs, only cVFs, only lcVFs and cVFs and lcVFs combined was significant ($p<0.0001$).

Table 6.1 *Baseline characteristics*

	All patients	**No VF**	**Only common location**	**Only less common location**	**Both locations**	**P-value[a]**
	N = 1237	N = 998	N = 139	N = 42	N = 58	
Age (mean, SD)	61.3 8.0	60.7 8.0	63.6 7.3	63.8 7.0	64.9 7.1	<0.0001
Men (N, %)	756 61.1	582 58.3	97 69.8	34 81.0	43 74.1	0.0003
BMI (mean, SD)	25.8 4.5	25.8 4.5	26.2 4.7	25.6 4.8	24.2 4.0	0.04
Height (mean, SD)	170.1 9.1	169.8 9.1	171.4 8.9	171.4 7.5	171.0 8.7	0.12
Weight (mean, SD)	74.8 15.8	74.6 15.6	77.5 17.1	75.4 15.1	71.3 14.7	0.07
COPD (N, %)	997 80.6	795 79.7	118 84.9	32 76.2	52 89.7	0.12
Former smoker (N, %)	713 57.6	560 56.1	90 64.7	30 71.4	33 56.9	0.07
Current smoker (N, %)	524 42.4	438 43.9	49 35.3	12 28.6	25 43.1	
Pack years (mean, SD)	43.3 24.8	42.3 23.6	46.2 29.1	50.8 30.6	47.5 27.6	0.03
Sum vertebral fractures (T_4-T_{12}: N, %)						<0.0001
0	998 80.7	998 100.0				
1	139 11.2		104 74.8	35 83.3		
2	63 5.1		32 23.0	7 16.7	24 41.4	
>2	37 3.0		3 2.2		34 58.6	
BA (mean, SD)	155.6 47.5	162 46.3	138 44.3	122 35.1	110 36.1	<0.0001

Common locations: T_7, T_8, T_{11}, T_{12}; less common locations: T_4-T_7, T_9, T_{10}

Abbreviations: VF = vertebral fracture; SD = standard deviation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; BA = bone attenuation

[a] Differences between groups were assessed using ANOVA for continuous variables and chi-square test for categorical data

Local BA per vertebra according to VFs locations

BA gradually decreased from T_4 to T_{12}, for both subjects without as well as subjects with at least one VF (Figure 6.3A). Therefore, we additionally analysed local BA in each individual non-fractured vertebra. Local BA was at any level significantly lower in the group of subjects with at least one prevalent VF compared to subjects without prevalent VFs, after adjustment for age and sex (Figure 6.3A).

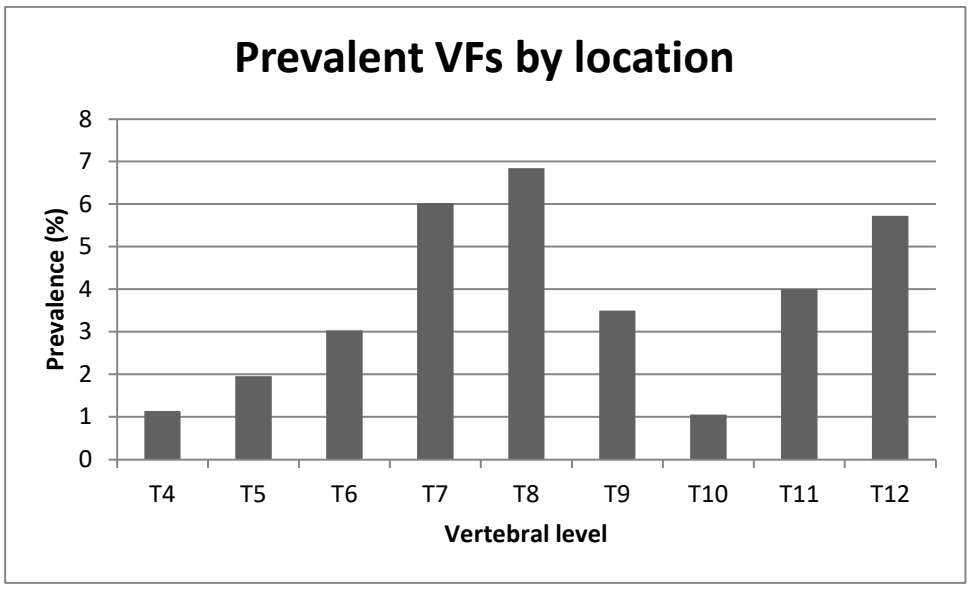
In Figure 6.3B**,** local BA is shown at each vertebral level for subjects without prevalent VFs, with only cVFs, only lcVFs or both cVFs and lcVF.

Linear regression analysis showed that, after adjustment for age and sex, at each vertebral level local BA was significantly lower comparing cVFs, lcVFs and both cVFs and lcVFs to the no VF group. At T_4, T_5, and T_6 there was a significant difference in BA between the only lcVF group and the only cVF group. The local BA of the cVF and lcVF combined group was significantly lower at each location, except T_8, as compared to the local BA of the only cVF group.

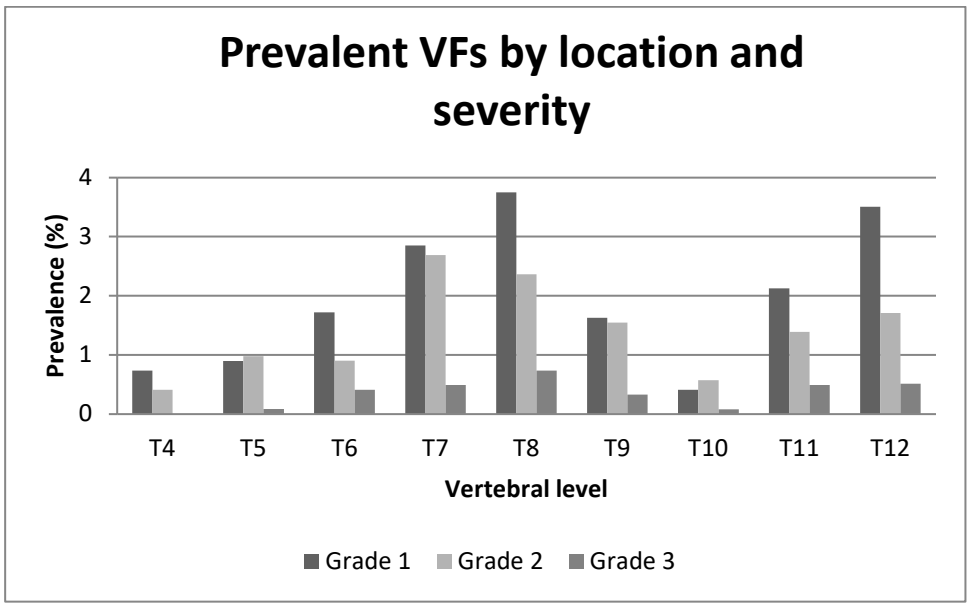
In Table 6.2, the ORs (adjusted for age and sex) for having any prevalent VF, only cVFs, only lcVFs or combined per -50 HU BA (approximately one standard deviation) are shown. Each 50 HU decrease of BA was associated with a 2.2-3.4 times greater odds of having a lcVFs. These ORs were higher than the odds of a cVFs (OR: 1.5-1.9) and were the highest for combined lcVFs and cVFs.

Load/BA ratio

In subjects with VFs the calculated load/BA ratio was higher 34% than in subjects without VFs ($p<0.0001$). In subjects with only cVFs (the most frequent and most loaded regions with a decreased BA of 15%), the load/BA ratio was significantly higher (+25%, $p<0.0001$) than in subjects without VFs. In subjects with both cVFs and lcVFs (having a 32% lower BA), the load/BA ratio was significantly higher (+63%, $p<0.001$) than in subjects without VFs. Thus, cVFs occurred in subjects with a higher BA and a lower load/BA ratio than in subjects with both cVFs and lcVFs.



1A



1B

Figure 6.1 *Proportion of prevalent VFs (**1A**) and prevalent VFs according to severity (**1B**) at vertebrae T_4-T_{12} on chest CT scans*

Abbreviations: VF = vertebral fracture

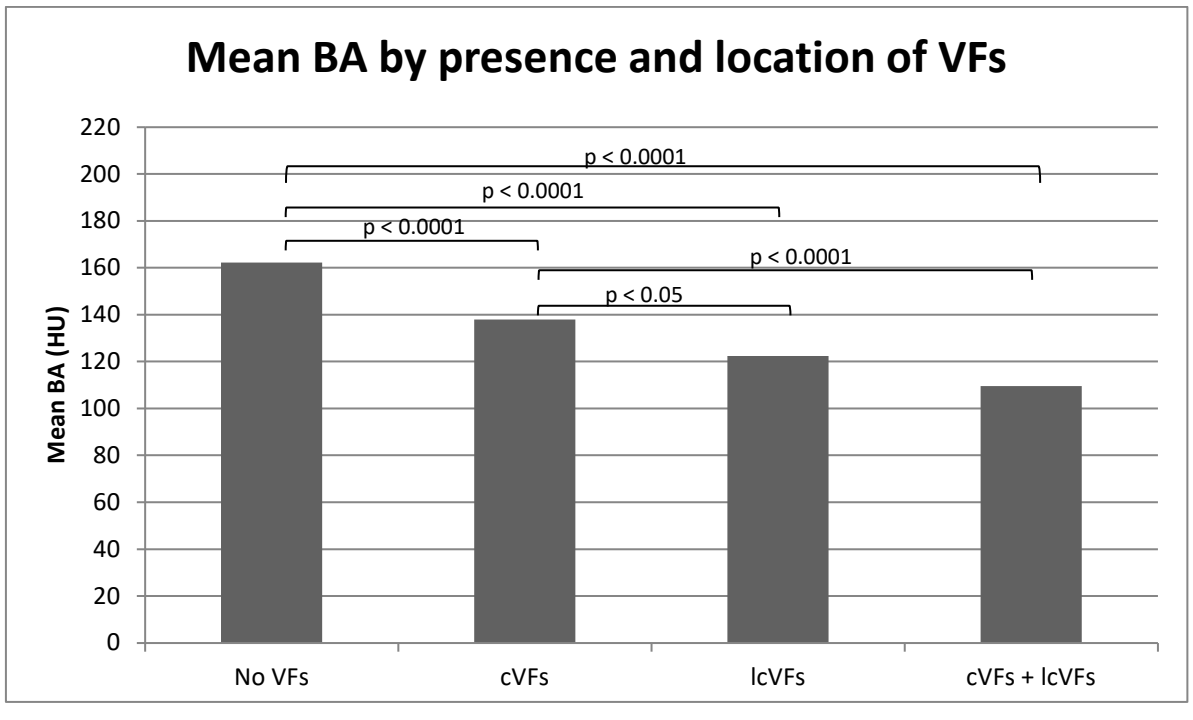


Figure 6.2 *Comparison of total BA between subjects without a VF and subjects with VFs according to the regions of VF locations*

Differences between groups were adjusted for age and sex. There was a significant trend in the gradual lower BA from no VFs towards cVFs and lcVFs combined.

Abbreviations: BA = bone attenuation; VF = vertebral fracture; cVF = prevalent vertebral fracture at common location (T_7-T_8, T_{11}-T_{12}); lcVF = prevalent vertebral fracture at less common location (T_4-T_6, T_9-T_{10})

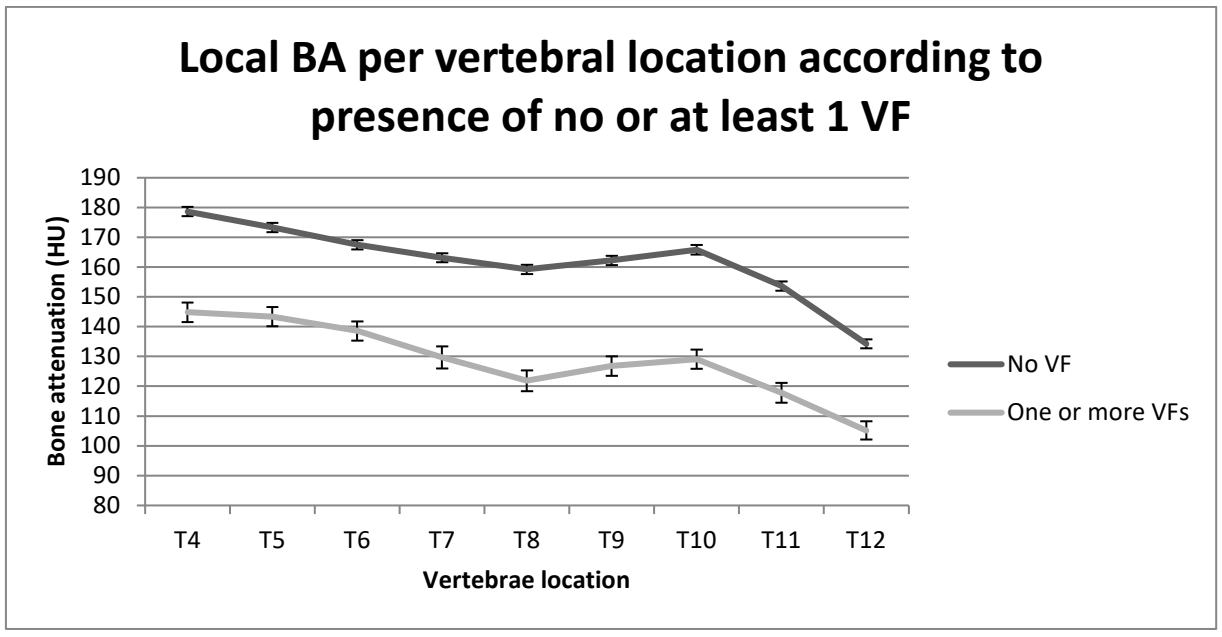


***Figure 6.3 A**) Mean (with standard error of the mean) local bone attenuation stratified by the presence of vertebral fractures, and **B**) Mean (with standard error of the mean) local bone attenuation stratified by the presence and location of vertebral fractures*

Abbreviations: VF = vertebral fracture; HU = Hounsfield Units;

cVF = prevalent vertebral fracture at common location (T_7-T_8, T_{11}-T_{12}); lcVF = prevalent vertebral fracture at less common location (T_4-T_6, T_9-T_{10})

Table 6.2 *Odds ratios for the presence of a VF per -50 HU in bone attenuation, stratified for VF locations*

	Outcome			
	At least one VF at any location	**At least one cVF**	**At least one lcVF**	**At least one cVF and one lcVF**
BA measured at location	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]	OR (95% CI)[a]
T_4	2.13 (1.77 – 2.55)	1.59 (1.27 – 1.99)	2.87 (1.94 – 4.24)	3.84 (2.65 – 5.56)
T_5	2.08 (1.71 – 2.51)	1.51 (1.20 – 1.90)	2.79 (1.85 – 4.20)	4.30 (2.84 – 6.52)
T_6	2.02 (1.65 – 2.46)	1.43 (1.14 – 1.80)	3.35 (2.03 – 5.54)	4.20 (2.76 – 6.41)
T_7	2.19 (1.76 – 2.72)	1.62 (1.23 – 2.13)	2.74 (1.87 – 4.02)	4.03 (2.45 – 6.62)
T_8	2.49 (1.97 – 3.14)	1.93 (1.41 – 2.63)	2.84 (1.93 – 4.18)	3.94 (2.40 – 6.49)
T_9	2.21 (1.81 – 2.70)	1.78 (1.40 – 2.26)	2.38 (1.56 – 3.61)	4.57 (2.91 – 7.19)
T_{10}	2.12 (1.77 – 2.56)	1.63 (1.30 – 2.04)	2.21 (1.53 – 3.20)	4.43 (3.00 – 6.57)
T_{11}	2.42 (1.94 – 3.02)	1.79 (1.35 – 2.37)	2.86 (1.90 – 4.30)	4.40 (2.81 – 6.87)
T_{12}	2.24 (1.74 – 2.87)	1.49 (1.09 – 2.06)	3.20 (1.98 – 5.17)	3.86 (2.36 – 6.32)

[a] *Adjusted for age and sex*

Abbreviations: VF = vertebral fracture; HU = Hounsfield units; OR = odds ratio; CI = confidence interval; cVF = prevalent vertebral fracture at common location (T_7-T_8, T_{11}-T_{12}); lcVF = prevalent vertebral fracture at less common location (T_4-T_6, T_9-T_{10})

Discussion

Our data showed that total BA in the thoracic spine was significantly lower in subjects with at least one VF. In addition, total BA was significantly lower in subjects with only lcVFs compared to subjects with only cVFs. The odds for a prevalent VF per decrease of 50 HU in BA varied according to VF location with the lowest OR for cVFs, higher ORs for lcVFs and highest ORs for cVFs and lcVFs combined.

The bimodal distribution of prevalent VFs with clustering in two peaks (T_7-T_8 and T_{11}-T_{12}) was similar as in a Dutch population-based cohort study based on a random sample and the Fracture Intervention Trial in the US.[7,31] Subjects with VFs had lower total and local BA than subjects without a VF. This is in line with the finding that subjects with VFs have lower BMD in the lumbar spine or hip[2,32] and that prevalent VFs are associated with micro-architectural deterioration in the distal radius and tibia measured by HR-pQCT.[33] This indicates that prevalent VFs are associated with generalized bone fragility throughout the axial and peripheral skeleton.

Our main finding was that the associations between BA and VFs differed according to the location of VFs. Previous studies have shown that associations between BMD and VFs differ according to VF locations. Two studies reported a stronger association between BMD and upper spine VFS than with lower spine VFs.[7,8] One study reported a lower BMD in subjects with only VFs outside T_{12}-L_1 compared to subjects with only VFs in T_{12}-L_1.[9] However, these studies did not report the associations between BMD and VFs according to both locations with the highest prevalence of VFs. Our results indicate that lcVFs occur in subjects with a more fragile thoracic spine than subjects with the most prevalent cVFs. This is further supported by the higher ORs for the presence of VFs per one SD lower BA per vertebra in subjects with only lcVF than in subjects with only cVFs.

Thus, the degree of vertebral bone fragility varies between subjects according to the thoracic spine locations of VFs. The heterogenous structural failure throughout the thoracic spine can thus not be explained by BA. The most frequent VFs are found in subjects with a higher BA than in subjects with lcVFs. As with any bone that fractures, vertebrae are likely to fracture when the load imposed on the bone exceeds the bone strength.[34] However, the load on vertebrae differs according to their location.

In a retrospective study of 562 patients with a traumatic fracture of the spine, 219 (39%) had occurred after a fall, predominantly at T_{11} (4%), T_{12} (14%) and L_1 (29%).[14] Thus, in the presence of a clear acute trauma such as a fall, VFs occur by preference at the thoracolumbar junction and less in other spine regions. This cannot be explained by bone fragility, as subjects with only T_{11}-T_{12} VFs in the VERO trial had higher BMD (in spine and hip) than patients with VFs at other locations and subjects with these VFs in our study had higher BA than subjects with lcVFs.[9]

Remarkably however, and in contrast to non-vertebral fractures, most VFs do not occur after a fall or overt trauma, and do not present with the acute clinical signs and symptoms of a fracture.

Such VFs are reported as subclinical,[35] spontaneous,[13] a-traumatic or non-traumatic,[36] or are detected incidentally in population surveys.[31]

The question than arises which other factors than a fall or a severe trauma could explain the presence of subclinical VFs and its bimodal distribution over the spine. An interesting observation is that the load distribution throughout the spine is unequal during activities that increase the load on the vertebrae.[10] During more strenuous daily activities (bending, twisting with weight in hands, lifting weights, pushing), compression loads are highest in common VF locations.[10] Interestingly, in subjects with only cVFs, we found that BA was only slightly decreased (-15%) compared to subjects without a VF. This suggests that these VFs are mainly associated with high compression loads related to such more strenuous activities that then exceeds the slightly decreased bone strength.

In contrast, in subjects with the combination of cVFs and lcVFs, BA was much lower (-32%). In such cases the load/strength ratio of vertebrae is exceeded mainly in association with a lower BA. Even with daily activities of minor compression loads are than associated with VFs, at common and less common levels.

Interestingly, we also identified a group of subjects with only lcVFs. As less-strenuous loads that occur in the less common fracture levels (due to e.g. walking, getting up from a chair, tying shoes when sitting) still occur at normal magnitudes, these subjects could be more susceptible to VF only in these less-common regions. One example is that shear load on vertebrae is higher in T_6-T_{10} than in T_{11}-T_{12}.[29]

Thus, cVFs occurred in subjects with a higher BA and a lower load/BA ratio than in subjects with both cVFs and lcVFs, suggesting a combined role of BA and load in the location of VFs. However, the interpretation of these indirect calculations needs to be interpreted with caution and will need studies that combine the measurement of load and BA in the same subjects.

Briggs et al.[37] found that subjects with a VF had significantly greater normalised compression ($p=0.0008$) and shear force ($p<0.0001$) profiles and hypothesised that greater segmental flexion moments, compression forces and shear forces would exist in individuals with an osteoporotic vertebral fracture compared to those with osteoporosis and no history of vertebral fracture.

It is well known that assessment of VF status in addition to BMD provides relevant clinical information in predicting fracture risk.[38] The clinical implication our finding is that subjects with lcVF have lower BA and may be at even higher fracture risk than subjects with only cVFs. The further useful clinical information is that BA alone cannot explain the locations of VFs, and that differences in load/BA ratio need further study to understand the heterogeneous locations of VFs. Our findings also contribute to further studies that investigate why most VFs are not accompanied by the acute signs and symptoms of an acute fracture and why most of the VFs occur subclinical, without overt acute trauma.

This study has several limitations.

First, this study was performed in smokers with and without COPD. Therefore, the results cannot be generalized to other populations, as smoking and COPD are independent risk factors for VFs and have different pathophysiology as compared to postmenopausal women and elderly.[39,40] However, the peaks of prevalent VFs were similar as found in population studies in postmenopausal women and in men.

Second, we only evaluated BA non-fractured VFs, as BA can be increased following fracture healing with callus formation and thus not reflect its pre-fracture BA.

Third, we evaluated BA within the central region of the vertebrae. Intravertebral BA measured by QCT is significantly correlated with *in vitro* compressive strength of the vertebrae.[41-43]

Fourth, we had no data on fall or trauma history, so we could not evaluate whether a VF was the result of a fall or other trauma or whether they occurred subclinical.[44] We neither have data on the level of physical activity.

Fifth, we did not evaluate adjacent intervertebral disc height and kyphosis angles that also influence how compressive forces are distributed over the vertebral body.[15]

Sixth, the different CT scanners were not cross-calibrated, which may have influenced our results. Also differences between scanner manufacturers were not investigated for this study. However, scanners were regularly calibrated using industry and institutional standards. Although asynchronous calibration using a phantom or internal phantomless calibration is advocated when using different CT scans, in a review it was cited that some have suggested using the CT values directly without any calibration to BMD.[45]

Seventh, we did not measure lumbar spine vertebrae, as they are not included on chest CT scans.

Due to these limitations further studies will be needed that integrate load and BA to explore the reasons of unequal distribution of VF in the spine.

In conclusion, the association between VFs and BA differs according to the location of VFs and ORs increases from subjects with cVFs only, to subjects with lcVFs and were the highest in subjects with cVFs and lcVFs combined, indicating that other factors than only BA play a role in the bimodal distribution of VFs. Prospective studies will be needed that examine the association between BA in non-fractured vertebrae at baseline and the incidence of new VFs according to their location.

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Chapter 7

Association between vertebral fractures and coronary artery calcification in current and former smokers in the ECLIPSE cohort

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Abstract

Introduction - Prevalence of VFs among smokers and patients with chronic obstructive pulmonary disease (COPD) is high, and an association between CAC and osteoporosis has been described. We investigated the associations between VFs and CAC (expressed in Agatston score) in (former) smokers.

Methods - Current and former smokers from the ECLIPSE study (designed to determine underlying COPD progression mechanisms) were studied. Baseline Agatston score (zero (0), medium (1-400), or high (> 400)), baseline bone attenuation (BA), and prevalent and incident VFs (vertebrae T_1-L_1) were assessed on CT.

Results - A total of 586 subjects were included (mean age 59.8 ± 8.3; 62.3% men; 70.1% with COPD; 21.0% with prevalent VFs; 196 with zero, 266 with medium, and 124 with high Agatston score). Of these, 23.4% suffered incident VFs within 3 years. In multivariate models, prevalent VFs were associated with medium (1.83 [95% CI 1.01-3.30]) and with high (OR = 3.06 [1.45-6.47]) Agatston score. After adjustment for BA, prevalent VFs were still associated with high (OR = 2.47 [1.13-5.40]), but not significantly with medium Agatston score (OR = 1.57 [0.85-2.88]). Similarly, after adjustment for BA, high (OR = 2.06 [1.02-4.13]) but not medium Agatston score (OR = 1.61 [0.88-2.94]) was associated with prevalent VFs. Agatston score at baseline was not associated with short-term VF incidence.

Conclusion **-** In (former) smokers, there was an association between prevalent VFs and Agatston score. Chest CT scans provide the opportunity to also evaluate for VFs and CAC, which are potentially important comorbidities, each of which is amenable to effective interventions.

Keywords Agatston score; COPD; Comorbidity; Coronary artery calcification; Smoking; Vertebral fracture.

Introduction

Reported prevalence of vertebral fractures (VFs) among smokers and COPD patients is high (9-79%[1-7]) and, in the international ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort, we previously reported that short-term incidence of VFs is high in smokers and former smokers with one or more prevalent VF.[8] A recent review described an association between cardiovascular disease (CVD) and osteoporosis,[9] and suggested the potential benefits from routine bone assessment in patients with CVD. Associations between emphysema and osteoporosis or bone density have also reported.[4,10,11] An association between emphysema and coronary artery calcification (CAC) has been reported in some studies[12,13] but not in others.[14-16]

Although CAC itself may be clinically asymptomatic, it is associated with coronary heart disease in patients without known CHD,[17-19] cardiovascular disease,[20] cardiac events,[21] and mortality.[22-24] Also in a population of (former) smokers (National Lung Screening Trial (USA)), CAC was associated with CHD death and all-cause mortality.[25] Calcification in the coronary arteries is related to the underlying plaque burden, and calcifications in the coronary arteries, aortic arch, and carotid arteries are correlated (moderate to strong).[26]

Chest CT scans are regularly performed to evaluate pulmonary disease and can be used to diagnose emphysema. Additionally, CT scans give the opportunity to evaluate the bone status (bone attenuation (BA) and VFs) and CAC (expressed in Agatston score).

Therefore, the aim of this study was to evaluate the associations between variables measured on chest CT scans in current or former smokers from the ECLIPSE cohort:

a) the association between prevalent VFs and baseline Agatston score;
b) the association between baseline Agatston score and prevalent VFs; and
c) the association between baseline Agatston score and incident VFs within one and three years

Methods

Subjects

The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study is a non-interventional multicentre study that was started to search underlying mechanisms of disease progression in subjects with COPD, and to identify biomarkers that may serve as surrogate endpoints and measures of disease progression (Clinicaltrials.gov identifier NCT00292552; GlaxoSmithKline study SCO104960).

Detailed inclusion and exclusion criteria were described elsewhere.[27-29] In brief, current or former smokers (40-75 years old) with moderate to very severe COPD (Global Initiative for

Chronic Obstructive Lung Disease (GOLD) stage II-IV) or without COPD, with a smoking history of at least 10 pack-years were included. Subjects with respiratory diseases other than COPD, patients with α1-antitrypsin deficiency, with known history of significant inflammatory disease other than COPD, with an exacerbation requiring treatment within four weeks prior to enrolment, or subjects who used oral glucocorticosteroids (GC) at baseline were excluded.

Measurements

Demographic and pulmonary information were collected as well as number of pack-years and smoking status. Detailed information can be found elsewhere.[27-29]

CT scans were performed at full inspiration (120 kV peak, 40 mAs, 1.00 or 1.25-mm volumetric acquisition, General Electric or Siemens), at baseline, one-year and three-year follow-up. CT scanners were calibrated regularly using industry and institutional standards. Emphysema, VFs, BA and Agatston score were measured on these CT scans.

Emphysema was measured as % low attenuation area (%LAA), as described by Coxson et al.[30] Presence of emphysema was defined by a cut-off value of >10%LAA.[30]

Sagittal reformats containing the spine were superposed to create simulated lateral X-ray images. VFs from T_1 to L_1 were semi-quantitatively, and subsequently quantitatively (using SpineAnalyzer morphometry software; Optasia Medical, Cheadle, UK[31-33]) assessed on the three-year follow-up images. VFs were classified according to the method by Genant et al. as grade 1 (mild), grade 2 (moderate) or grade 3 (severe).[34] If VFs were diagnosed on the three-year scan, the one-year scan was morphometrically assessed. If VFs were diagnosed on the one-year scan, the baseline scan was also evaluated. Incident VFs were defined as new (no VF to any grade of VF) or worsening VFs (increase in grade of VF) as previously described.[8]

BA was measured semi-automatically in cubic areas of approximately 275 mm^3 (slightly varying due to different voxel sizes between scanners) centred in vertebrae T_4-T_{12}. Mean BA of vertebrae T_4-T_{12} was expressed in Hounsfield Units (HU). Vertebrae that were fractured (grade 1 or higher[34]) or that showed other abnormalities were excluded from BA measurements.

Agatston score measurements are described in detail elsewhere.[15,35] Areas of ≥1 mm^3 with a threshold of ≥130 HU in the course of a coronary artery were considered CAC. Agatston score was calculated as the sum of weighted areas (depending on peak attenuation within the area) on axial slices. Three groups were made based on Agatston score at baseline: zero (0 Agatston Units (AU)), medium (1-400 AU) or high Agatston score (>400 AU).

Main outcome measure

The main outcome measures were

a) prevalent Agatston score (main factor: prevalent VFs),
b) prevalent VFs (main factor: prevalent Agatston score), and
c) incident VFs within one and three years (main factor: prevalent Agatston score)

Possible confounders that were considered included age, sex, BMI, smoking status (current/former), number of pack-years, presence of COPD, emphysema (>10%LAA), and in case of incident VFs, prevalent VFs at baseline. Since associations between BA and Agatston score,[36] and between BA and fractures[1,37] have been reported, BA was included as a potential confounder.

Statistics

a) Association between prevalent VFs and baseline Agatston score

A chi-square test was used to compare the proportion of patients with a prevalent VF between the Agatston score groups. Logistic regression models (SAS 9.3, SAS Institute, Cary, NC, USA; LOGISTIC procedure) were used to evaluate the association between prevalent VFs (no VF, or ≥1 VF) and Agatston score group (zero: 0 AU, medium: 1-400 AU, or high: >400 AU). To compare medium vs. zero Agatston score group, only subjects with medium or zero Agatston score were included in the analyses. To compare high vs. zero Agatston score, only subjects with high or zero Agatston score were included.

b) Association between baseline Agatston score and prevalent VFs

To evaluate the association between Agatston score and prevalent VFs, logistic regression models including all subjects were used.

c) Association between Agatston score and incident VFs within one and three years

A chi-square test was used to compare the proportion of patients with an incident VF between the Agatston score groups. To evaluate the association between Agatston score and incident VFs, Cox proportional hazard models were used (PHREG procedure). When incident VFs were expressed in numbers of incident VFs (0, 1, or ≥2), a nominal regression model was used (LOGISTIC procedure).

Confounders

Age, sex, and presence of COPD were included in all multivariate models; other confounders were included in the multivariate model if they independently changed the beta-coefficient of the main exposure (*a)* prevalent VFs; *b)* Agatston score group; *c)* incident VFs) by 5% or more, or previously reported associations indicated that they should be included.

Odds ratios (ORs) and Hazard ratios (HRs) are given with [95%CI]. Subjects with complete availability of VF assessment and Agatston score evaluation were selected. Only 1 subject (0.2%) had missing data and was excluded from further analyses.

Results

Out of a total of 2298 ECLIPSE subjects (327 subjects without and 1971 with COPD), there were 586 subjects (411 with and 175 without COPD) with Agatston score and VF assessment available (Table 7.1).[8] Of the patients with a zero Agatston score, 20 (10.2%) had one or more prevalent VFs, compared to 61 (22.9%) in the medium Agatston score group and 42 (33.9%) in the high Agatston score group (Figure 7.1). The proportion of patients with a prevalent VF was significantly different across the Agatston score groups (p-value <0.001). Of the patients with a zero Agatston score, 40 (20.4%) had one or more incident VFs within three years, compared to 60 (22.6%) in the medium Agatston score group and 37 (29.8%) in the high Agatston score group. The proportion of patients with an incident VF over three years increased (but not significantly) across the Agatston score groups (p-value: 0.14).

Association between prevalent VFs and baseline Agatston score

Of the subjects with one or more prevalent VF, 20 (16%) had zero Agatston score, 61 (50%) had medium Agatston score and 42 (34%) had high Agatston score. In subjects without prevalent VFs, these numbers were 176 (38%), 205 (44%) and 82 (18%) respectively (supplemental Figure 7.1).

Table 7.1 *Baseline characteristics*

	All subjects n = 586		**Zero Agatston group** n = 196		**Medium Agatston group** n = 266		**High Agatston group** n = 124	
Age (years: mean, sd)	59.8	8.3	55.0	7.6	60.8	7.7	65.3	6.1
Sex (M: n, %)	365	62.3	93	47.4	176	66.2	96	77.4
BMI (kg/m2: mean, sd)	26.1	4.3	26.0	4.6	26.2	4.0	26.0	4.2
With COPD (n, %)	411	70.1	106	54.1	200	75.2	105	84.7
Current smoker (n, %)	275	*46.9*	111	56.6	115	43.2	49	39.5
Pack-years (mean, sd)	41.1	24.0	32.8	18.8	44.1	24.8	47.6	26.2
Emphysema >10%LAA (n, %)	263	44.9	66	33.7	130	48.9	67	54.0
Bone attenuation (HU: mean, sd)	158.4	46.5	174.9	43.4	154.0	42.6	141.5	51.2
≥1 prevalent VF (n, %)	123	21.0	20	10.2	61	22.9	42	33.9
Incident VF within one year (n, %)	57	9.7	14	7.1	22	8.3	21	16.9
Incident VF within three years (n, %)	137	23.4	40	20.4	60	22.6	37	29.8

Baseline characteristics for all subjects, and by Agatston score group

Zero: 0 Agatston Units (AU); Medium: 1-400 AU; High: >400 AU

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; %LAA = % low attenuation area; HU = Hounsfield Units; VF = vertebral fracture

In univariate models, subjects with prevalent VFs had higher odds of a medium (OR: 2.62 [1.52-4.51]) or high Agatston score (OR: 4.51 [2.49-8.16]) compared to subjects without VFs (Table 7.2). In multivariate models, subjects with prevalent VFs had higher odds of having a medium (1.83 [95%CI 1.009-3.304]) or high (OR=3.06 [1.45-6.47]) Agatston score compared to subjects without VFs. After additional adjustment for BA, subjects with prevalent VFs still had higher odds of high (OR=2.37 [1.06-5.31]), but not of medium Agatston score (OR=1.56 [0.84-2.90]).

In univariate models, odds of medium or high Agatston score for subjects with emphysema (>10%LAA) were 1.88 [1.29-2.76], but this was not significant after adjustment for age and sex.

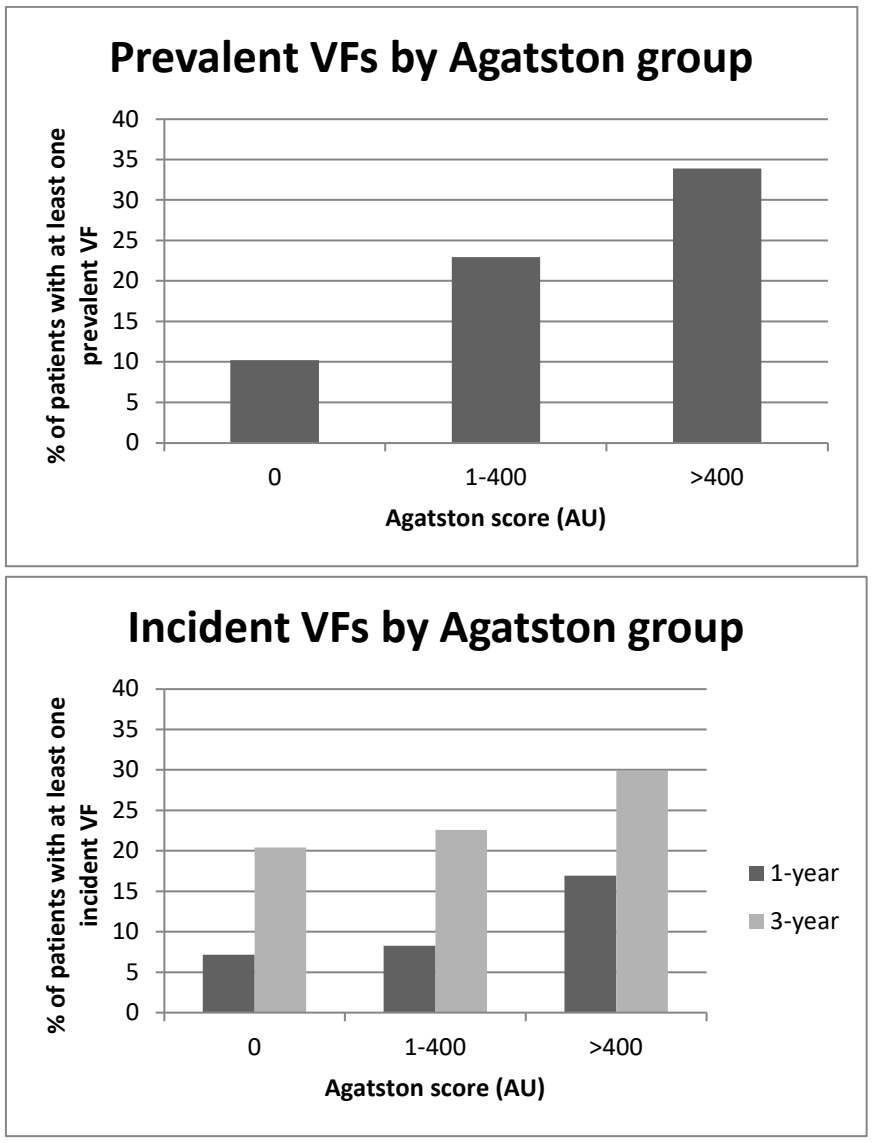

Figure 7.1 *Proportion of patients with a prevalent VF (top panel) or 1 or 3 years-incident VF (lower panel) stratified by Agatston score*

Abbreviations: AU: Agatston units; VF: vertebral fracture

Table 7.2 *Association between prevalent VFs and Agatston score*

	Univariate		**Multivariate, without BA**		**Multivariate, with BA**	
	OR	95%CI	OR	95%CI	OR	95%CI
Medium Agatston score						
Age (per +8 year)	**2.16**	**[1.750-2.654]**	**1.84**	**[1.446-2.332]**	**1.67**	**[1.296-2.150]**
Sex (M vs F)	**2.17**	**[1.484-3.162]**	**1.79**	**[1.183-2.703]**	**1.85**	**[1.220-2.808]**
BMI (per +4 kg/m^2)	1.05	[0.879-1.243]	-		-	
Current smoker (vs former)	**0.58**	**[0.402-0.846]**	-		-	
Pack-years (per +24 pack year)	**1.95**	**[1.502-2.537]**	**1.37**	**[1.041-1.791]**	**1.39**	**[1.060-1.828]**
COPD (vs no COPD)	**2.57**	**[1.733-3.821]**	1.26	[0.781-2.030]	1.27	[0.788-2.062]
BA (per -46 HU)	**1.68**	**[1.367-2.072]**	-		**1.30**	**[1.024-1.664]**
≥1 prevalent VF (vs none)	**2.62**	**[1.520-4.510]**	**1.83**	**[1.009-3.304]**	1.57	[0.853-2.883]
Emphysema (vs. 'no emphysema')	**1.88**	**[1.286-2.757]**	-		-	
High Agatston score						
Age (per +8 year)	**4.81**	**[3.373-6.854]**	**3.97**	**[2.718-5.809]**	**3.69**	**[2.512-5.412]**
Sex (M vs F)	**3.80**	**[2.290-6.297]**	**2.75**	**[1.473-5.118]**	**3.08**	**[1.616-5.885]**
BMI (per +4 kg/m^2)	1.01	[0.828-1.241]	-		-	
Current smoker (vs former)	0.50	[0.317-0.791]	-		-	
Pack years (per +24 pack year)	**2.17**	**[1.610-2.914]**	**1.60**	**[1.124-2.272]**	**1.57**	**[1.099-2.237]**
COPD (vs no COPD)	**4.69**	**[2.670-8.244]**	1.39	[0.665-2.916]	1.38	[0.657-2.886]
BA (per -46 HU)	**2.12**	**[1.630-2.751]**			**1.43**	**[1.031-1.971]**
≥1 prevalent VF (vs none)	**4.51**	**[2.490-8.158]**	**3.06**	**[1.450-6.473]**	**2.47**	**[1.128-5.403]**
Emphysema (vs. 'no emphysema')	**2.32**	**[1.460-3.671]**	-		-	

Significant ORs are in bold format. For continuous variables, ORs are given per standard deviation of the total population. Multivariate: confounders included according to >5% rule (age, sex, and presence of COPD were included in all models). Reference group is the zero Agatston score group.

Abbreviations: OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index; COPD = chronic obstructive pulmonary disease; BA = bone attenuation; HU = Hounsfield Units; VF = vertebral fracture; %LAA = % low attenuation area

Association between baseline Agatston score and prevalent VFs

Characteristics of subjects with (n=123) or without (n=463) prevalent VFs are given in Table 7.3. In univariate models, subjects with medium (2.62 [1.52-4.51]) or high Agatston score (4.51 [2.49-8.16]) had higher odds of having a prevalent VF compared to subjects with a zero Agatston score. In multivariate models, subjects with medium (OR=1.91 [1.07-3.40]) or high Agatston score (OR=2.71 [1.40-5.26]) had significantly increased odds of having a prevalent VF compared to subjects with a zero score. After additional adjustment for BA, subjects with high but not medium Agatston score had significantly higher odds of prevalent VFs than subjects with a zero score (OR=2.03 [1.01-4.08] and OR=1.60 [0.88-2.92] respectively, Table 7.3).

Association between baseline Agatston score and incident VFs within one and three years

There were 57 subjects (9.7%) with incident VFs within one year, and 137 (23.4%) within three years after baseline (Table 7.1). Of the subjects with one or more incident VFs within three years, 40 (29.2%) had zero Agatston score, 60 (43.8%) had medium Agatston score and 37 (27%) had high Agatston score. In subjects without incident VFs, these numbers were 156 (35%), 206 (46%) and 87 (19%) respectively (supplemental Figure 7.2).

In univariate models, subjects with high prevalent Agatston score had a significantly increased risk of one-year VF incidence (HR=2.37 [1.21-4.66]), but of the higher three-year incidence risk was not significant (HR=1.46 [0.94-2.29]). In multivariate models, subjects with medium or high prevalent Agatston score had no significantly increased VFs risk and this was mainly due to the effect of adding prevalent VFs, age, and BA to the model. However, subjects with a prevalent VF and, in case of three-year incidence, also subjects with lower BA had increased risk of VF incidence.

When the number of incident VFs (0, 1, or ≥2) was taken as outcome measure, there were significant univariate associations between subjects with high Agatston score and ≥2 incident VFs (one year OR=9.72 [2.11-44.72]; three year OR=3.79 [1.64-8.73]), but in multivariate models this was no longer significant.

Table 7.3 *Association between Agatston score and prevalent VFs*

	Without VF		**With VF**			**Univariate**		**Multivariate, without BA**		**Multivariate, with BA**	
	n = 463		n = 123			OR	95%CI	OR	95%CI	OR	95%CI
Age (years: mean, sd)	59.1	8.3	62.6	7.7	*per +8 year*	**1.55**	**[1.255-1.907]**	1.24	[0.983-1.572]	0.97	[0.743-1.255]
Sex (M: n, %)	267	57.7	98	79.7	*M vs F*	**2.88**	**[1.787-4.633]**	**2.28**	**[1.394-3.741]**	**2.87**	**[1.707-4.812]**
BMI (kg/m^2)	26.1	4.3	26.0	4.0	*per +4 kg/m^2*	0.97	[0.803-1.169]	-		-	
Current smoker (n, %)	224	48.4	51	41.5	*vs Former smoker*	0.76	[0.505-1.130]	-		-	
Pack-years (mean, n)	39.6	23.5	46.6	25.3	*per +24 pack year*	**1.30**	**[1.080-1.555]**	1.08	[0.886-1.320]	1.09	[0.881-1.351]
COPD (n, %)	317	68.5	94	76.4	*vs no COPD*	1.49	[0.942-2.365]	-		-	
BA (HU: mean, sd)	165.8	45.2	130.2	40.3	*per -46HU*	**2.60**	**[2.008-3.375]**	-		**2.54**	**[1.899-3.400]**
Emphysema (>10%LAA: n, %)	201	43.4	62	50.4	*vs 'no emphysema'*	1.32	[0.890-1.973]	-		-	
Zero Agatston group (n, %)	176	38.0	20	16.3				-		-	
Medium Agatston group (n, %)	205	44.3	61	49.6	*vs Zero Agatston score*	**2.62**	**[1.520-4.510]**	**1.91**	**[1.069-3.396]**	1.60	[0.876-2.915]
High Agatston group (n, %)	82	17.7	42	34.1	*vs Zero Agatston score*	**4.51**	**[2.490-8.159]**	**2.71**	**[1.389-5.264]**	**2.03**	**[1.013-4.080]**

Significant ORs are in bold format. For continuous variables, ORs are given per standard deviation of the total population. Multivariate: confounders included according to >5% rule (age, sex, and having COPD included in all models).

Abbreviations: VF = vertebral fracture; OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index; COPD = chronic obstructive pulmonary disease; BA = bone attenuation; HU = Hounsfield Units; %LAA = % low attenuation area

Table 7.4 *Association between Agatston score group and incident VFs*

	Univariate		Multivariate, without BA		Multivariate, with BA	
	HR	95%CI	HR	95%CI	HR	95%CI
ONE YEAR INCIDENCE						
Age (per +8 year)	**1.49**	**[1.129-1.954]**	1.25	[0.897-1.737]	1.17	[0.827-1.645]
Sex (M vs F)	**2.05**	**[1.107-3.815]**	1.43	[0.738-2.749]	1.46	[0.757-2.831]
BMI (per +4 kg/m^2)	0.84	[0.652-1.082]	0.90	[0.690-1.177]	0.96	[0.726-1.269]
Current smoker (vs former)	0.95	[0.561-1.592]	1.28	[0.716-2.296]	1.32	[0.736-2.367]
Pack-years (per +24 pack year)	1.21	[0.977-1.489]	1.07	[0.825-1.379]	1.07	[0.827-1.382]
COPD (vs. no COPD)	1.78	[0.925-3.446]	0.86	[0.352-2.077]	0.87	[0.357-2.106]
Emphysema (>10%LAA, vs ≤10%LAA)	**2.11**	**[1.234-3.620]**	1.89	[0.936-3.805]	1.85	[0.913-3.740]
BA (per -46 HU)	**1.79**	**[1.337-2.395]**			1.27	[0.910-1.785]
≥1 prevalent VF (vs none)	**3.93**	**[2.338-6.607]**	**3.19**	**[1.830-5.553]**	**2.75**	**[1.523-4.970]**
Medium Agatston score (vs Zero)	1.16	[0.595-2.272]	0.69	[0.335-1.425]	0.67	[0.323-1.373]
High Agatston score (vs Zero)	**2.37**	**[1.206-4.662]**	1.05	[0.481-2.279]	0.97	[0.444-2.130]
THREE YEAR INCIDENCE						
Age (per +8 year)	**1.24**	**[1.046-1.466]**	1.12	[0.916-1.378]	1.05	[0.847-1.297]
Sex (M vs F)	**1.70**	**[1.161-2.484]**	1.33	[0.890-1.998]	1.37	[0.915-2.060]
BMI (per +4 kg/m^2)	0.92	[0.784-1.080]	0.97	[0.817-1.152]	1.03	[0.859-1.226]
Current smoker (vs former)	1.11	[0.798-1.558]	1.37	[0.939-2.006]	1.40	[0.956-2.039]
Pack-years (per +24 pack year)	1.09	[0.939-1.274]	0.97	[0.811-1.165]	0.98	[0.816-1.173]
COPD (vs. no COPD)	1.40	[0.940-2.075]	1.15	[0.686-1.931]	1.16	[0.690-1.939]
Emphysema (>10%LAA, vs ≤10%LAA)	0.74	[0.526-1.028]	1.24	[0.812-1.891]	1.22	[0.796-1.862]
BA (per -46 HU)	1.56	[1.302-1.878]			**1.29**	**[1.034-1.598]**
≥1 prevalent VF (vs none)	**3.50**	**[2.503-4.892]**	**3.30**	**[2.307-4.713]**	**2.84**	**[1.944-4.152]**
Medium Agatston score (vs Zero)	1.11	[0.741-1.649]	0.76	[0.494-1.180]	0.73	[0.472-1.129]
High Agatston score (vs Zero)	1.46	[0.935-2.287]	0.80	[0.479-1.335]	0.74	[0.441-1.241]

Significant HRs are in bold format. For continuous variables, HRs are given per standard deviation of the total population. Multivariate: confounders included according to >5% rule (age, sex, and having COPD included in all models).

Abbreviations: VF = vertebral fracture; HR = hazard ratio; 95%CI = 95% confidence interval; BMI = body mass index; COPD = chronic obstructive pulmonary disease; %LAA = % low attenuation area; BA = bone attenuation; HU = Hounsfield Units

Discussion

In this study, we found an association between prevalent VFs and high Agatston score on chest CT scans in (former) smokers with and without COPD. Associations between Agatston score and incident VFs were not significant in multivariate models. The clinical consequence is that when chest CT scans are performed in (former) smokers to evaluate pulmonary function, supplementary evaluation of the presence of VFs and the degree of CAC gives information on risk factors for other diseases for which additional treatment can be considered.

In line with an earlier review,[9] we found significant independent associations between BA, prevalent VFs, and high Agatston score. An association between VFs and Agatston score is consistent with the reported correlation of FRAX-estimated risk of hip fracture or major osteoporotic fracture with CAC score.[38] Some linking mechanisms have been proposed, such as an association between micro- and macro-vessel damage and altered microarchitectural indices in the radius,[39] or between decreased vascular flow in the lower extremities and increased rate of bone loss at the hip and calcaneus in older women.[40] We suggest that the association between CAC and VFs in part may be explained by the shared risk factor of smoking.

Vascular calcifications in the aorta are commonly seen in patients with osteoporosis, and both increase with aging and with renal disease. Possibly related to renal disease, vascular smooth muscle cells can secrete inhibitors of wnt-signalling that lower bone formation rates. It has been postulated that low bone formation rates fail to buffer high mineral loads and could thus predispose to vascular calcification.

Current smokers had lower odds of having a medium (Table 7.2, OR=0.58 [0.40-0.85]) or a high (OR=0.50 [0.32-0.79]) Agatston score compared to former smokers. This may seem unexpected, but in this population former smokers were significantly older (62.3 ±7.1 vs. 57.0 ±8.7), more often had COPD (84.9% vs 53.5%), and had lower BA (154.0 ±45.3 vs 163.2 ±47.4) as compared to current smokers.

There were relatively fewer women (n=221) than men (n=365) included in this study. A lower percentage of women had a prevalent VF than men in this subcohort (11.3% vs. 26.8%), as reported in our previous study (14.1% vs. 24.5%).[8] In addition, women less often had medium (40.7%) or high Agatston score (12.7%) than men (48.2% and 26.3% resp.), resulting in very few women with VF and high Agatston score (n=6 (3%)).

When analyses regarding the associations between Agatston score and VFs were performed for men and women separately, the associations for men were similar as presented. However, the associations in women were not significant; not surprisingly given the small number of women in the high risk group. However, it is possible that the women included in this study do not represent the female COPD and smoker population (selection bias) and/or that the association between CAC and VFs is different in men and women.

The literature has been contradictory about the association between emphysema and CACS; some studies found an association between emphysema and CAC,[12,13] while others did not.[14-16] Although we found a univariate association between emphysema and medium or high Agatston score (Table 7.2), this association was not significant after adjustment for age and sex.

Although there was a significant univariate association between high Agatston score and one-year incidence, and between high Agatston score and ≥2 incident VFs within one and three years, we did not find any significant multivariate associations between Agatston score and incident VFs after adjusting for age, sex, BA, and prevalent VFs.

A recent meta-analysis examined data from prospective cohort studies of aortic calcification and fractures.[41] Although not all individual studies found significant results, it was reported that subjects in the high aortic calcification category had increased fracture risk compared to subjects in the zero category. However, when types of fractures were specified, Wei et al. reported that the association with incident VFs was not significant, consistent with our findings. They also reported a significant association with incident hip fractures, for which we do not have data. In our results, prevalent VFs (associated with high Agatston score (Table 7.2 and 7.3)) and to a lesser extent baseline BA were significantly associated with incident VFs, also consistent with previous findings.[37] The significant association between high Agatston score and incident VFs disappeared after adjustment. The point estimate shifted towards one which suggests that there is no association between Agatston score measured at baseline and the risk of incident VFs within one year. Moreover, there was also no association with incident VFs over three years.

In multivariate models, we found an association between prevalent VFs and high Agatston score. Therefore, we suggest all current and former smokers diagnosed with either osteoporosis, a prevalent VF or coronary artery calcification should be evaluated for the osteoporosis or coronary artery disease respectively. Given the relative simplicity of measuring the Agatston score on the chest CTs, we suggest this measurement should be routinely performed and reported and high levels should trigger further assessments including of bone attenuation and coronary artery disease.

There are several limitations in this study.

First, there is a chance of a selection bias due to inclusion of subjects for the ECLIPSE study, and selection of subjects from the ECLIPSE study. For the ECLIPSE study, subjects were recruited from outpatient clinics, and subjects with mild COPD (GOLD stage I) or who were using oral GC at baseline were excluded. In addition, only non-Hispanic whites were included. From the ECLIPSE study, only subjects with availability of the complete VF assessment[8] and Agatston score evaluation[15] were included for this study. Subjects included (n=586) were somewhat younger, had lower BMI, less often had COPD, more often were current smokers, and less often

had emphysema (>10%LAA) compared to all ECLIPSE subjects (n=2298). For characteristics of included subjects (n=586) and total ECLIPSE population (n=2298) see Supplementary Table 7.1, online supplement.

VF data were only available from vertebra T_1-L_1, so information on prevalent or incident VFs in L_2-L_5 is lacking. Also, due to the design of the ECLIPSE study information on other risk factors for fractures, such as the history of falls and fractures, family history of other fractures (including hip fracture), presence of rheumatoid arthritis or other metabolic disorders were not available, and could not be used for adjustment of models for incident VFs. Lastly, Agatston score was only measured at baseline and follow-up data concerning Agatston score are not available.

Conclusion

In this study of current and former smokers from the ECLIPSE study, we have shown a significant association between prevalent VFs and Agatston score, underlining the concept of multiple comorbidities in this patient group. This indicates that in clinical practice, (former) smokers who are assessed for and diagnosed with either VFs or CAC, should be screened for the other. Since VFs and Agatston score can be diagnosed in CT scans made for pulmonary evaluation, we also recommend opportunistic evaluation of these scans for VFs and CACs as potentially important comorbidities, each of which is amenable to effective interventions.

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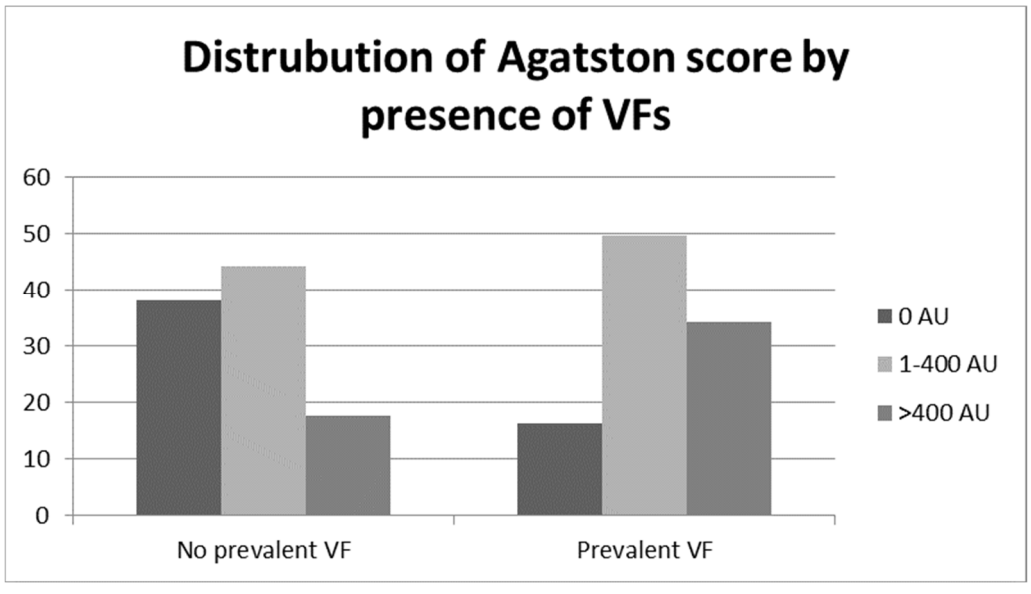
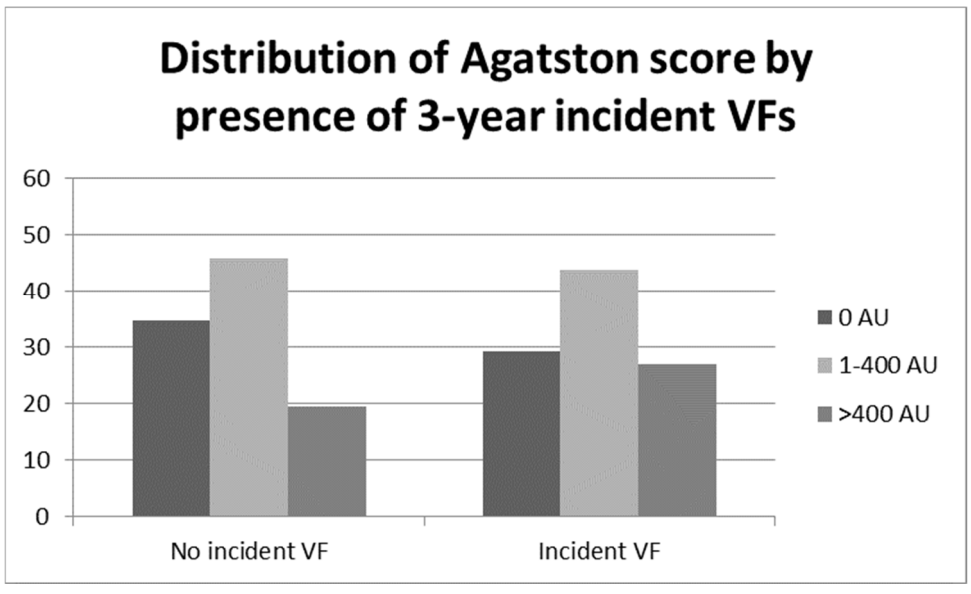
Supplementary material



Supplementary Figure 7.1 *Distribution of Agatston score by the presence of VFs at baseline*
Abbreviations: AU: Agatston units; VF: vertebral fracture



Supplementary Figure 7.2 *Distribution of Agatston score by the presence of three year incident VFs*
Abbreviations: AU: Agatston units; VF: vertebral fracture

Chapter 8

Summary

This thesis focusses on the clinical implications of systematic vertebral fracture assessment on chest computed tomography (CT) scans in smokers with or without chronic obstructive pulmonary disease (COPD). The data presented in this thesis are primarily obtained from the ECLIPSE study. The ECLIPSE (Evaluation of COPD longitudinally to identify predictive surrogate endpoints) study is a non-interventional multicentre international study following patients with COPD over three years, to search underlying mechanisms of disease progression in subjects with COPD, and to identify biomarkers that may serve as surrogate endpoints and therefore could measure disease progression (Clinicaltrials.gov identifier NCT00292552; GlaxoSmithKline study SCO104960). A unique feature in the ECLIPSE study is that chest CT scans were obtained at baseline, after one year and after three year with CT scanners that were used in clinical practice. For this thesis we systematically evaluated bone attenuation (BA) and vertebral fractures (VFs) on chest CT scans at baseline, one- and three-year follow-up among the participants with and without COPD of the ECLIPSE study. We specifically aimed to study the associations between clinical determinants such as age, sex, smoking status, smoking history, CT-measured BA and thoracic kyphosis with prevalent and incident VFs. Additionally, we aimed to study the associations between BA and VF location and the association between VFs and coronary artery calcification (CAC) in this specific population.

Although the gold standard for VF diagnosis is a lateral X-ray image, VFs can also be diagnosed on chest CT or lateral dual-energy X-ray absorptiometry (DXA) images. In clinical practice, these three imaging techniques are often applied, but radiological reports on diagnosed deformities may not always be congruent. In **chapter 2**, we studied the level of agreement for diagnosis of vertebral deformities from T_4 to L_1 on chest CT scans, lateral dual-energy X-ray absorptiometry (DXA) images of the spine and lateral X-ray images of the thoracic spine (the current gold standard for assessment of vertebral deformities according to the Dutch guideline). This study was performed in a population of 87 subjects (57% males, 66% with COPD) that participated in a clinical trial related to osteoporosis in COPD patients (NCT01067248) at the Catharina Hospital (Eindhoven, the Netherlands) using SpineAnalyzer^{TM} morphometry software (Optasia Medical, Cheadle, UK).

After excluding vertebrae that were not evaluable because of anomalies or other deformities, we applied the criteria of Genant et al. to quantify the deformities based on the measured height loss as no deformity (height loss <20%: grade 0), mild deformity (20% ≤ height loss < 25%: grade 1), moderate deformity (25% ≤ height loss < 40%: grade 2) or severe deformity (height loss ≥40%: grade 3).

We found that intraclass correlation coefficient (ICCs) for vertebral height measurements were excellent (>0.94) ant that Kappa's were good to excellent (0.64–0.77). For vertebral deformities fractures, sensitivity (51%–73%) and positive predictive values (57%–70%) were fair to good for all three modalities and specificity and negative predictive value were excellent (≥96%). We concluded that the performance of chest CT and to a lesser extent of lateral DXA images

indicated that these imaging techniques could be used for assessment of vertebral deformities in COPD patients.

Subsequently, in **chapter 3** we evaluated the prevalence and the one- and three-year incidence of VFs on chest CT scans in 1239 subjects of the ECLIPSE population (61% male, 81% with COPD). In this population, 253 subjects (20.5%) had ≥1 prevalent VF, and the cumulative incidence of VFs was 10.1% within one and 24.0% within three years. After adjustment for age, sex, body mass index (BMI), pack-years, and smoking status, prevalence and incidence were similar between smokers and COPD GOLD stages. Importantly, after one year, 29.2% of the subjects with a prevalent VF had an incident VF, compared with 5.1% in absence of a prevalent VF. The risk of incident VFs within one year and three years (hazard ratio (HR): 5.1, 95% confidence interval (CI) [3.6-7.4]) and 3.6, 95% CI [2.9-4.6] respectively) was therefore strongly associated with the presence of prevalent VFs. In addition, VF risk was higher with number and severity of prevalent VFs, and subjects with an incident VF within the first year had a high risk of a subsequent incident VF within the two following years.

In this study, more than half of the smokers and subjects with COPD with a prevalent VF or an incident VF within the first year sustained a subsequent VF within three years, indicating that (former) smokers with or without COPD with a prevalent VF or recent incident VF have a high imminent VF risk.

In **chapter 4**, we further studied the association between BA and prevalent VFs on chest CT scans and the risk of incident VFs among the (former) smokers with and without COPD from the ECLIPSE study. BA was measured semi-automatically in regions of interest (ROIs) of approximately 275 mm^3 in vertebrae T_4 to T_{12} (fractured vertebrae were excluded from measurements) using a self-written algorithm in Matlab and expressed in Hounsfield Units (HU).

We observed that subjects with a prevalent VF had a significantly lower BA compared to subjects without prevalent VFs (155.6±47.5 HU vs. 162.6±46.2 HU). BA and prevalent VFs were significantly associated with one- and three-year VF incidence, while age, sex, BMI, smoking status, smoking history, and presence of COPD were not. These results, based on systematic evaluation of chest CT scans suggest that the combination of BA and prevalent VFs was strongly associated with the short-term risk of incident VFs in smokers with or without COPD.

It is known that the presence of VFs in the thoracic spine often leads to increased thoracic kyphosis and in computational models it had been shown that greater kyphosis angles lead to increased loading on vertebral bodies. However, the association between severity of kyphosis

and VF incidence in patients was largely unknown. In **chapter 5**, we therefore studied the association between prevalent VFs and severity of kyphosis, and the association between severity of kyphosis and incident VF risk using chest CT scans form 1239 ECLPISE study participants. We measured kyphosis angles between vertebrae T_4 and T_9, and between T_4 and T_{12}. Although kyphosis was measured in supine position on the chest CT images, this study showed that the presence, number and severity of VFs were associated with greater kyphosis angles. The mean increase in kyphosis angle within three years was small, but significantly greater in subjects with incident VFs compared to those without. After adjustment for BA and prevalent VFs, a greater baseline kyphosis angle was independently associated with incident VFs within one and three years (HR 1.34, 95% CI [1.12-1.61] and 1.29, 95% CI [1.15-1.45], respectively). These findings support the theory that greater kyphosis angle contributes to higher biomechanical loads in the spine.

In addition to kyphosis angles, also daily activities influence loading on the vertebral bodies. It has been suggested that loading during daily activities is highest in the vertebra T_7-T_8 and T_{11}-T_{12}, suggesting these vertebrae could be at higher fracture risk. Indeed, most VFs are observed in the mid-thoracic and thoracolumbar areas of the spine. In **chapter 6**, we hypothesised that VFs in the areas that bear the highest loadings during daily activities, the most common VFs (T_7-T_8 and T_{11}-T_{12}), occur at higher BA than VFs in less common locations (T_4-T_6 and T_9-T_{10}). Baseline chest CT images of T_4-T_{12} in smokers with and without COPD from the ECLIPSE study were analysed for the presence of VFs according to the method described by Genant. BA, expressed in Hounsfield units (HU), was measured in all non-fractured vertebrae.

Compared to subjects without prevalent VFs, there was a gradually lower BA for subjects with VFs only at the common locations (cVFs; -15%), VFs only at the less common locations (lcVFs; -25%, $p<0.05$ vs. cVFs) and VFs at both common and less common locations (-32%, $p<0.0001$ vs. cVFs) (all $p<0.0001$ compared to subjects without VF, $p<0.0001$ for trend). At each vertebral level from T_4 to T_{12}, a lower BA was associated with cVFs (OR between 1.5-1.9 for each 50 HU lower BA), lcVFs (OR between 2.2-3.4) and both lcVFs and cVFs (OR between 3.8-4.6). These findings suggest the contribution of BA to the load/strength ratio of vertebrae differs between vertebral locations and that other factors besides BA, such as vertebral load during daily activities or caused by a fall, may determine the location of a VF.

In **chapter 7**, we evaluated the association between VFs and CAC, given the high prevalence and incidence of VFs we found in chapter 3 and the fact that smoking is also strongly associated with cardiovascular events. Of 586 participants in the ECLIPSE study, (62% male, 70% with COPD) we systematically evaluated the presence of VFs and CAC. VFs were categorised according to the method described by Genant and CAC was expressed in Agatston score and categorised as zero, medium (1-400) and high (>400). Of all subjects, 21% had a prevalent VF

and 23% had an incident VF within three year, and 196 subjects (33%) had low, 266 subjects (45%) had medium (1-400), and 124 subjects (21%) had high (>400) Agatston scores.

Prevalent VFs were associated with medium and high Agatston score (OR = 1.83, 95% CI [1.01-3.30] and 3.06, 95% CI [1.45-6.47], respectively). After adjustment for BA, prevalent VFs were still associated with high (OR = 2.47 [1.13–5.40]), but not with medium Agatston score. Agatston score at baseline was not associated with short-term VF incidence. These findings indicate that in clinical practice, (former) smokers with or without COPD, who are assessed for and diagnosed with either VF or CAC, should be screened for the other.

Given the high prevalence and incidence of VFs in COPD subjects, we propose to systematically evaluate the presence of VFs at chest X-ray or chest CT scans made for pulmonary evaluation. Improvement in patient care can be achieved by increasing awareness among pulmonologists and radiologists about the clinical importance for recognizing VFs. Patients with VFs should be further evaluated and treated according to local osteoporosis and fracture prevention guidelines.

Chapter 9

General discussion

In this thesis, we evaluated the clinical implications of systematic vertebral fracture (VF) assessment on chest computed tomography (CT) scans in smokers with or without chronic obstructive pulmonary disease (COPD). We first studied the level of agreement for diagnosis of VFs on chest CT scans, lateral dual-energy X-ray absorptiometry (DXA) images and lateral X-ray images (**chapter 2**). Subsequently we studied the prevalence and three-year incidence of VFs in smokers with and without COPD based on systematic evaluation of chest CT images from the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) participants (**chapter 3**). We further studied associations between bone attenuation (BA, a measure of bone density) and prevalent VFs on chest CT scans and the risk of incident VFs in the ECLIPSE population (**chapter 4**). In addition, associations between prevalent VFs and thoracic kyphosis angles, and between thoracic kyphosis angles and incident VFs were studied (**chapter 5**). In a subpopulation of the ECLIPSE study, we further assessed whether there are predilection locations of prevalent VFs, and whether this was associated with BA of individual vertebrae (**chapter 6**). Finally, we evaluated associations between VFs and coronary artery calcification (CAC) in a subpopulation of the ECLIPSE study (**chapter 7**). In this chapter, main findings of this thesis and their clinical implications, limitations and future perspectives will be discussed.

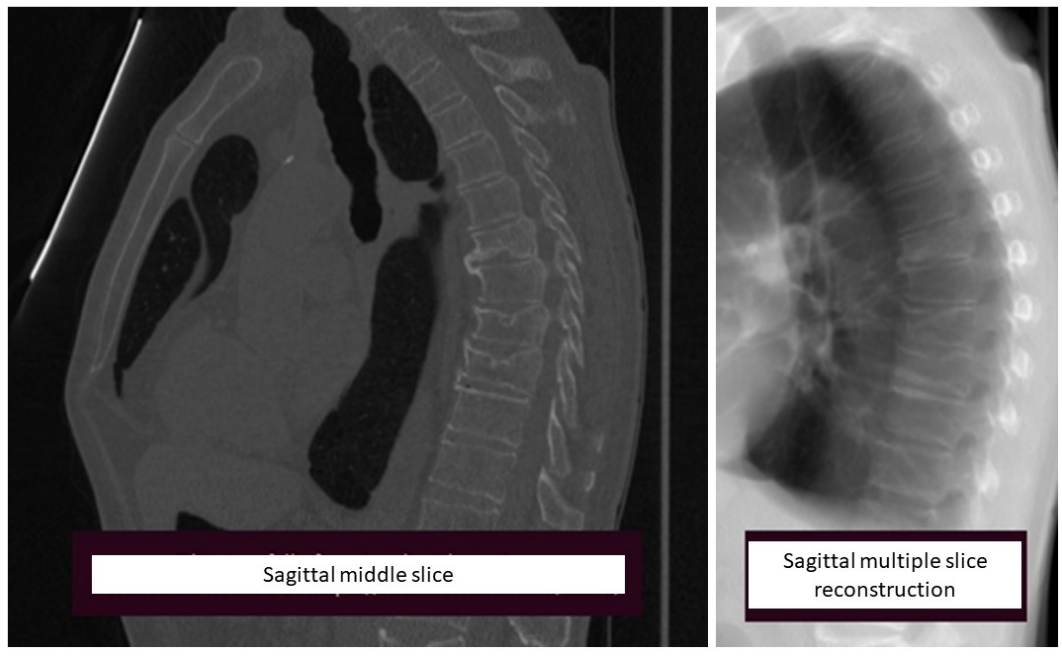
Algorithm for evaluation of vertebrae from chest CT scans

For all studies presented in this thesis, we first developed an algorithm for evaluation of vertebrae from chest CT scan images. We applied a morphometric VF assessment on vertebrae T_4-L_1 of the chest CT images. In **chapter 2**, we compared the diagnostic performance of chest CT, lateral X-ray and lateral DXA images.

Processing of the chest CT scans and image generation

We developed a method in Matlab (R2013a, MathWorks, Natick, MA, USA) to adapt the chest CT images to make them suitable for VF assessment, and to measure BA and kyphosis.

Of all sagittal CT reformats containing the spine, the contrast was adjusted to (partly) eliminate soft tissue. Subsequently, all sagittal reformats containing the spine were superposed to create simulated lateral X-ray 2D images (see Figure 9.1a and 9.1b for examples). The same was done to create a frontal view of the spine. Images were exported in DICOM format for VF assessment.



1a

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Figure 9.1 *Examples of the superposed sagittal reconstructions at the right, with the referral sagittal middle reconstruction (slice) from the CT scan*

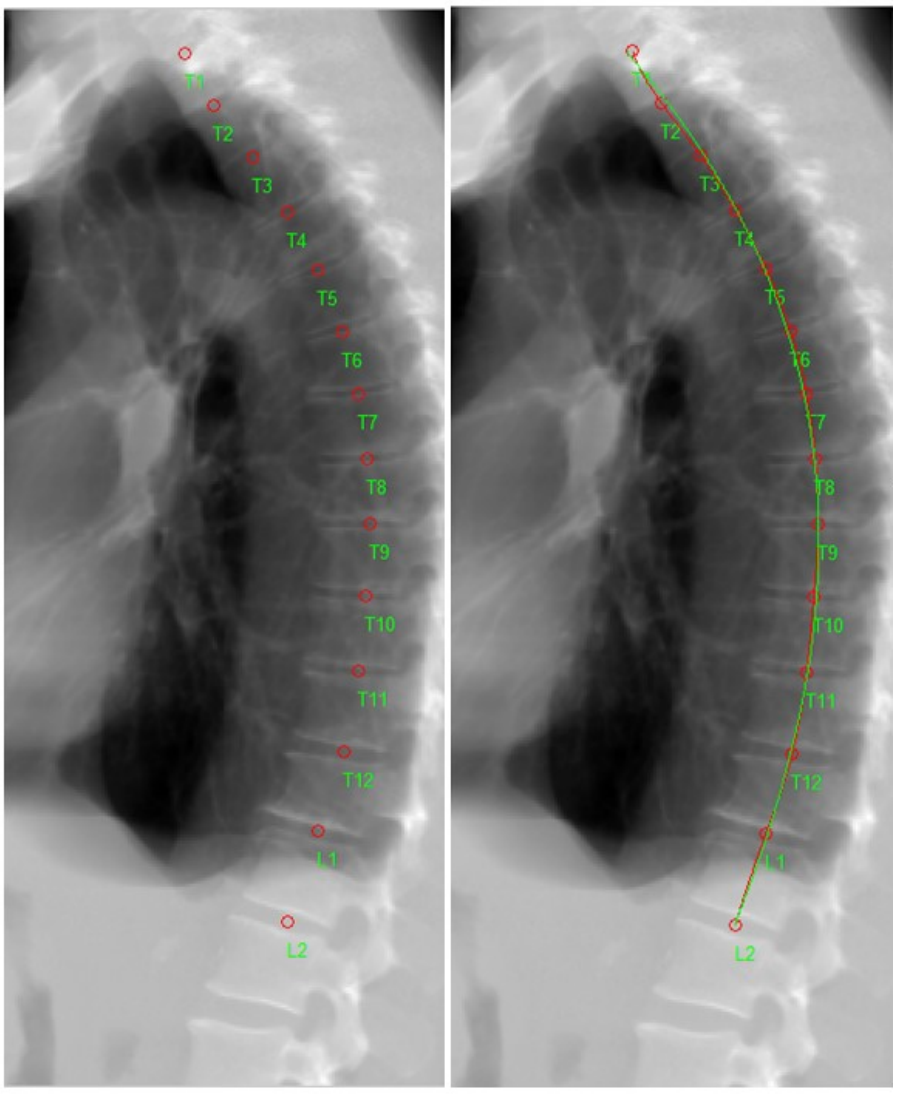

Figure 9.2 *User-indicated points (red) are placed centred in the intervertebral disks. The red line connects all user-indicated points, the green line represents the second order polynomial fit though the spine, describing the curvature of the spine.*

In case of sufficient quality (range of the image large enough to contain at least T_2-T_{10}, no movement artefacts in the spine, no major artefacts caused by metal objects within the scan, and no large scoliotic deformations), points centred in the intervertebral disks were placed by an experienced operator in the sagittal and frontal views. These points were used by the algorithm for measuring bone attenuation (BA) and kyphosis (see also Figure 9.2).

Assessment of bone attenuation

BA was measured in a region of interest (ROI) of approximately 275 mm^3 centred in vertebrae T_4 to T_{12} and expressed in Hounsfield Units (HU). The ROIs were placed by the algorithm based on the user-indicated points centred in the intervertebral disks.

Fractured or deformed vertebrae (based on visual inspection by the operator, or confirmed VFs after VF assessment) were excluded from BA measurements.

Kyphosis angles

To measure kyphosis angles, a 3rd order polynomial was fit through the spine based on the user-indicated points centred in the intervertebral disks (see Figure 9.3). Kyphosis was measured as the angle between two lines perpendicular to the polynomial, crossing the polynomial closest to the user-indicated points in the intervertebral disks. The angles between T_4 and T_9 (lines crossing polynomial in the intervertebral disks above T_4 and below T_9) and between T_4 and T_{12} (lines crossing above T_4 and below T_{12}) were measured.

Vertebral fractures

Apart from BA and kyphosis measurements, we inspected the CT images for the presence of VFs. The exported adapted sagittal 2D CT images were visually assessed for VFs from T_1 to L_1. A semiquantitative visual grading of vertebrae was performed, where vertebrae were graded as deformed or not deformed. Vertebrae with deformations due to qualitative features of morphology such as Schmorl's nodes, Scheuermann's disease, platyspondyly, or fusion of vertebrae were excluded from VF analyses. In case of height loss in the vertebral body at the anterior side, in the middle, or in the total vertebral body without other deformities, vertebrae were subsequently morphometrically assessed using the SpineAnalyzer software (Optasia Medical, Cheadle, UK).[2] This software automatically detects the vertebral shape (height and deformation) on lateral images based on user-indicated points centred in the vertebrae. All of the automatically detected points of the six-point morphometry were manually checked by one operator and adjusted if necessary. The vertebrae were classified based on height loss at posterior, middle, and/or anterior site, according to the method initially described by Genant and colleagues as no fracture (height loss <20%: grade 0), mild fracture (height loss 20% to <25%: grade 1), moderate fracture (25% to <40%: grade 2), or severe fracture (height loss 40% or more: grade 3).[3]

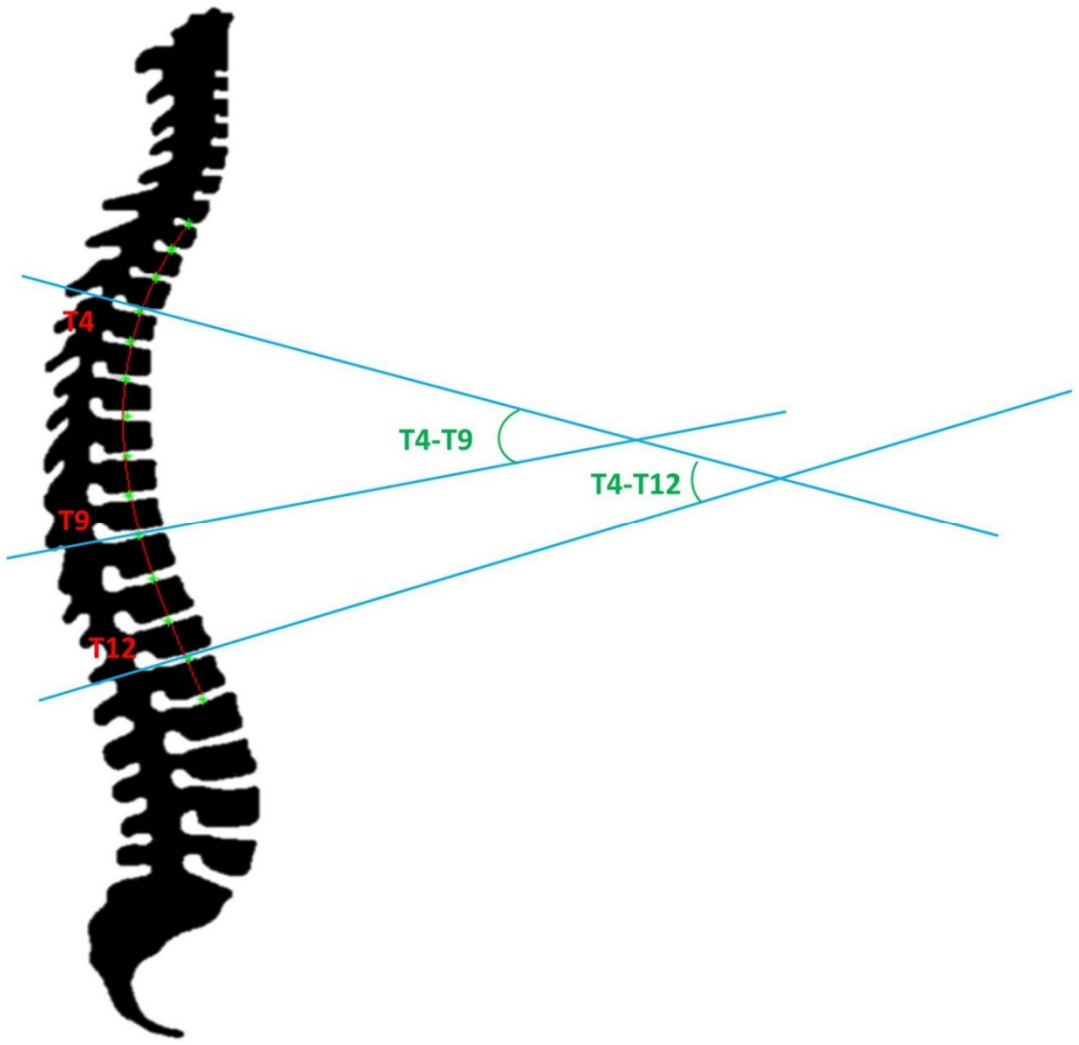

Figure 9.3 *Measurement of kyphosis angles (T_4-T_9 and T_4-T_{12}) by 3rd order polynomial, adapted from JBMR 2019*[1]

User-indicated points (green) were placed centred in the intervertebral disks, and a 3rd order polynomial (red) was fit through these points. The angle between T_4 and T_9 was measured as the angle between two lines (blue), above T_4 and below T_9, perpendicular to the 3rd order polynomial closest to the user-indicated points above T_4 and below T_9, respectively. The lines above T_4 and below T_{12} were used to measure the angle between vertebrae T_4 and T_{12}.

Technical considerations

Although kyphosis angles and BA were measured semi-automatically, and VFs were assessed using a validated software program, there are some technical considerations to keep in mind.

Bone attenuation

BA was measured in cubic ROIs that were automatically placed centred in the vertebrae based on user-indicated points in the intervertebral disks. The semi-automatic placement of the ROIs means that potential inhomogeneity of the bone structure within the vertebrae was not taken into account when measuring BA. Other methods to measure BA (although often measured in 2D) involve manual selection of the ROI, ensuring the placement of ROIs in a homogeneous area of the vertebrae. Although inhomogeneous tissue was not avoided in our measurements, the effect was probably minimal due to the volume of measured area; whereas manual measurements most often use <10 slices per patient[4-6] due to time consuming placement of ROIs, our BA measurements were based on 4 to 6 slices per vertebra (depending on slice thickness) and up to 9 vertebrae per subject. Vertebrae with obvious inhomogeneity due to for example a fracture or deformations were excluded from BA measurements.

There could be room for improvement in the shape of the ROI; in the method used we measured BA in cubic areas around a point centred in the vertebra, perhaps a spherical ROI would better fit the shape of the vertebrae since the cross-sectional shape of a vertebra is round rather than square. Also the cubic ROIs were placed aligned in the xyz-directions of the scan, not taking tilting of vertebrae relative to the scan into account. Since the ROIs were quite small (approximately 6.5 by 6.5 by 6.5 mm), it is not expected that changing the shape for the current setup will influence the measurements. However, shape change to better fit the vertebrae would also enable the possibility of using larger ROIs, which would result in BA measured in an even larger area. Additionally, all the ROIs had approximately the same size; perhaps size of the ROI could be adjusted based on size of the vertebra.

Kyphosis angles

The 3rd order polynomial was fitted in the sagittal (2D) plane, therefore curvature in the coronal plane did not influence the polynomial. A curvature in the coronal plane (scoliosis) may also influence VF risk, but the largest curvature in most subjects is found in the sagittal plane.

This method of measuring kyphosis is, to our knowledge, not used before in medical research. The mean r^2 for the degree of fit of the polynomial to the user-indicated points was 0.99 (range 0.9323-0.9998), and the ICC (intraclass correlation coefficient) of triple measurements of a

subset of n=25 scans was excellent (ICC>0.95, data not published). Therefore, we believe that our polynomial describes the curvature of the spine very well and that the method is reproducible. However, we have not studied the intra-operator variability.

Additional to the analysis of the fit of the polynomial and reproducibility of repeated measures, we compared the kyphosis angles as measured using our method with measuring kyphosis angles based on vertebral endplates using Surgimap software (Surgimap®, Nemaris Inc.™, New York, USA; available via www.surgimap.com). We found very good correlations for both the T_4-T_9 and the T_4-T_{12} angles (r^2>0.85; n=92 and n=77 for T_4-T_9 and T_4-T_{12} angles, respectively; data not published).

Even though the measured angles showed promising results when compared to the more often used angles measured between endplates, an important consideration is that the CT scans were taken with the subjects in supine position. It is expected that in standing position, gravitational forces influence thoracic kyphosis to a higher extend than in supine position, leading to an underestimation of the measured kyphosis when measured in supine position. However, studies comparing kyphosis angles in supine and in standing position showed that these measures are well associated.[7,8] Hence, although the severity of kyphosis may be underestimated when measured from images obtained in supine position (such as CT scans), these measurements could serve as alternative to images in standing positions to estimate kyphosis measurement.

Vertebral fractures

The simulated X-ray images by superpositioning the sagittal CT reformats in our model may provide more information than a single sagittal slice, but it is not a 3D image. Positioning of the subject (hence vertebrae) is therefore important for the image quality; due to the superpositioning of the sagittal slices, tilted vertebrae will result in unsharp endplates. Vertebrae do not have to be perfectly aligned to obtain good images, but the images of scoliotic patients will not be of sufficient quality. On the other hand, superpositioning of the sagittal CT reformats does not have the issue of beam divergence as is seen in traditional X-ray images, therefore making it possible to assess the endplates of the vertebrae in the image more adequately without oblique depicted vertebral bodies.

We have used the classification of VFs according to the method proposed by Genant.[3] Although other methods such as the ABQ method are available nowadays, the Genant classification is still the most often used method in clinical trials.

We assessed VFs on images based on CT scans and used morphometry software to assess VFs, which possibly has resulted in a more sensitive method to assess VFs than by visual inspection of X-ray images. In the absence of beam divergence and with use of morphometry software,

small height changes can be detected that could have resulted in higher VF grade, thereby possibly making CT in combination with morphometry software more sensitive.

We only have assessed VFs between T_1 and L_1 on the chest CT scans and therefore cannot say anything about prevalence and/or incidence of VFs in the lower lumbar part of the spine. Although most VFs occur in the mid-thoracic area of the spine,[9-14] it is very likely that not assessing L_2-L_5 has resulted in an underestimation, because of missing prevalent and/or incident VFs in the lumbar area.

Main findings of the thesis

Vertebral fracture assessment: diagnostic performance of chest CT, lateral X-ray and DXA images

As described in **chapter 2**, we showed that the reproducibility of vertebral fracture assessment by morphometric thoracic vertebral height measurements was very good on all three imaging modalities: chest CT, X-ray, and lateral DXA. The diagnosis of height loss and classification according to the method described by Genant et al.[3] on vertebral level resulted in a very high negative predictive value (NPV) but lower positive predictive value (PPV), especially for DXA. On subject level, diagnostic performance of CT was slightly better than for DXA.

When comparing DXA to X-ray images on a subject level, we found a lower sensitivity (69%) but comparable specificity (87%) compared to other studies (sensitivity 69–97%, specificity 74-100%).[15-23] The most important reason for the lower sensitivity of vertebral fracture diagnosis in our study is the fact that we only included vertebrae T_4 to L_1 in our study, because we wanted to evaluate the diagnostic performance in comparison with chest CT scans. The sensitivity of DXA for vertebral fracture diagnosis is generally reported to be lower in the upper thoracic area[17,23,24] compared to X-ray due to lower image quality especially in the upper thoracic levels.

Remarkably the PPV of CT was only 70 to 78% with lateral X-ray as gold standard modality. This actually reflects a false negative result of lateral X-ray, because we found more deformities (grade 1-3) on CT images. These findings suggest that CT might be a more sensitive method to diagnose vertebral deformities than the current gold-standard X-ray.

It should be noted that the subjects in this specific study population were selected for having either normal BMD or osteoporosis and that a large proportion of this population had COPD. It is expected that COPD patients (65.5% of our study population) and subjects with osteoporosis (46%) have a higher prevalence of VFs than healthy subjects. Prevalence of a condition (in this case VFs) does influence PPV and NPV, so our results can only be applied to populations with a similar prevalence of VFs. However, looking for vertebral deformities on medical images made for other indications is probably of more interest in patients with increased risk of VFs than in other populations, so in that scenario our study population represents the expected reality.

The findings in this study imply that all three imaging modalities can be used for the diagnosis of VFs of the thoracic spine. However, when applying the Genant classification for vertebral fractures based on height loss of the anterior, middle and posterior parts of vertebral body, the number of patients diagnosed with a vertebral fracture may vary and fractured vertebrae may be classified at different severity among the three techniques.

The prevalence and incidence of vertebral fractures in smokers with and without COPD

In Chapter 3, we investigated the prevalence and incidence of VFs in smokers with and without COPD. We found that 25% of all subjects (61% males, with a mean age of 61 years) had a prevalent VF and that the one- and three-year incidence was 10% and 24%, respectively. A prevalent VF at baseline was a major risk factor for incident VFs. After one and after three years, the incidence of VFs was 29.2% and 58.5%, respectively in subjects with a prevalent VF compared to 5.1% and 15.0% respectively in subjects without prevalent VFs, indicating that these subjects had a high imminent subsequent VF risk.

Although in multivariate models we found no difference in the risk of incident VFs between smokers with or without COPD and within subjects with COPD for GOLD stages, we have to keep in mind that the majority (999 out of 1239 (81%)) of the participants in the ECLIPSE cohort had COPD and that they were not treated with glucocorticoids (GCs) at baseline. This could imply that in the COPD population that is being treated with oral GCs, the risk of VFs could even be higher since there is a strong association between oral GC use and vertebral fractures.[25]

The increase of patients with prevalent VFs within three years (from just over 20% to over 30%) seems almost impressive, especially when keeping the group characteristics in mind (61 years, 61% male). However in a smaller group of male COPD patients, Graat-Verboom et al. found similar results within a three-year period.[26]

Apart from the increase in number of patients with a VF, more than half of the subjects with prevalent VFs were suffering from incident VFs within the course of our study. These numbers are underlining the importance of increase in awareness and treatment of VFs in (former) smokers and patients with COPD.

In **chapter 4**, we additionally studied the association of low bone density, evaluated by the mean BA of vertebrae T_4-T_{12} obtained from the chest CT images, with the incidence of VFs. We found that the combination of BA and prevalent VFs was strongly associated with the short-term incident VF risk; 1 SD lower BA resulted in a three year HR of 1.25, and presence of at least one prevalent VF resulted in a three year HR of 3.1, while age, sex, body mass index (BMI), smoking status and history, or presence of COPD were not significantly associated with incident VF risk.

It is known that VFs are associated with increased kyphosis, and additionally, increased kyphosis can contribute to increased fracture risk, even when adjusted for prior fracture history.[27,28] Therefore, we aimed to study associations between kyphosis angles and incident VFs after adjustment for BA and prevalent VF status in **chapter 5**. For the measurement of kyphosis angles we developed a new method, via a third-order polynomial fit through user-indicated points in the spine. Using this method, the measured angles describe the curvature of the spine rather than the influence of individual endplate deviations. We showed that a greater kyphosis angle at baseline was independently associated with increased risk of incident VFs within one and three years.

The associations we found support the hypothesis that the load-to-bone strength ratio is highest in the thoracolumbar area and during some activities in the high/midthoracic area and that the biomechanical effect of greater kyphosis angle could contribute to a higher load-to-bone strength ratio.

Finally in **chapter 6**, we performed an in-depth analysis by categorizing our study population in subjects without VFs, subjects having VFs at the most common locations (cVFs: T_7-T_8 and T_{11}-T_{12}), subjects having VFs at less common locations (lcVFs: T_4-T_6 and T_9-T_{10}), and subjects having VFs at both the most common locations and the less common locations.

We showed that there was a gradually lower BA for subjects with only cVFs (-15% compared to subjects without VF), only lcVFs (-25% vs no VFs) and both cVFs and lcVFs (-32% vs no VFs) and that the load/strength ratio of vertebrae differs between vertebral locations.

Most VFs do not occur after a fall or trauma, and do not present with the acute clinical signs and symptoms of a fracture. Such VFs are reported as spontaneous or subclinical and are often only detected incidentally. Therefore, the question arises which other mechanisms than acute trauma could explain the bimodal location of VFs. During more strenuous daily activities (bending, twisting with weight in hands, lifting weights, pushing), compression loads are highest in common VF locations.[29] Interestingly, we found that BA was only slightly lower (-15%) in subjects with only cVFs compared to subjects without a VF. This suggests that these VFs are mainly associated with high compression loads that exceed the slightly decreased bone strength.

In contrast, in subjects with the combination of cVFs and lcVFs, BA was much lower (-32%). In such cases the load/strength ratio of vertebrae is exceeded in the context of a lower BA. In these circumstances, even daily activities resulting in minor compression loads can cause VFs, at common and less common levels.

The data in **chapter 6** indicate that the contribution of BA to the load/strength ratio of vertebrae differs between vertebral locations and that besides BA, other factors such as vertebral load during daily activities or trauma, may determine the location of a VF. Prospective studies will be needed to examine the association between BA in non-fractured vertebrae at baseline and incident VFs during follow-up according to the location of incident VFs.

Data presented in **chapters 3** to 6 emphasize the high prevalence of VFs (22%) in relatively young smokers of whom 81% had COPD but were not using oral GC, and the high imminent subsequent VF risk in subjects with prevalent VFs, since more than half of them sustained subsequent VFs within three years. In multivariate analyses, subsequent fractures were associated with prevalent VFs and to a lesser degree with a lower BA and a greater kyphosis angle, but not with age, gender, COPD GOLD stages or other factors.

Interestingly these three factors (BA, prevalent VFs, and kyphosis angle) can directly be derived from the CT images. Therefore, the imminent risk of VFs in COPD patients and in heavy smokers can be assessed based on adequate analysis of the presence of a prevalent VF, BA and kyphosis angle on chest CT images. This opens a window of opportunity for improvement in clinical practice since this information can easily be obtained from the CT-scans so that adequate anti-osteoporosis treatment can be initiated especially in COPD patients and in heavy smokers with a prevalent VF.

Association between vertebral fractures and coronary artery calcification in smokers with and without COPD

An association between osteoporosis and cardiovascular disease (CVD) has been described in literature[30] and it has been suggested patients with CVD could potentially benefit from routine bone assessment. Although CAC itself may be asymptomatic, it has been reported to be associated with coronary heart disease, CVD, cardiac events, and mortality. In **chapter 6** we described an association between CAC expressed in Agatston score and prevalent VFs in a subset of smokers with and without COPD from the ECLIPSE study (586 subjects). We found that in multivariate models, high Agatston score (>400 Agatston units) and prevalent VFs were associated with each other, with ORs between 2.1 and 2.5 even after adjustment for BA (as a proxy for osteoporosis). However, we found no association between Agatston score and short-term VF incidence.

We suggest that the association between CAC and VFs in part may be explained by the shared risk factor of smoking. Given the relative simplicity of measuring the Agatston score and VFs on the chest CTs, we suggest these measurement should be routinely performed and reported and high levels of Agatston score and/or presence of VFs should trigger further assessments including of BA and CAC.

Methodological considerations

Additional to the technical considerations regarding our self-developed algorithm there are some methodological considerations related to the findings presented in this thesis.

Study cohorts

In **chapter 2**, results were based on a study population that was selected for having either normal BMD or osteoporosis (46%) and a large proportion (66%) of this population had COPD. It can be expected that COPD patients and subjects with osteoporosis have a higher prevalence of vertebral fractures than healthy subjects.

In **chapter 3 to 7**, results were based on the ECLIPSE study population. The ECLIPSE study was set up as a non-interventional multicentre international study to search for underlying mechanisms of disease progression in subjects with COPD, and to identify biomarkers that may serve as surrogate endpoints and therefore could measure disease progression. Therefore, a specific group of patients was selected, which may not truly reflect the COPD population as seen in clinical practice.

For example, one of the exclusion criteria was use of oral GC at baseline. Furthermore, the number of smokers without COPD was limited, and only a small proportion of the COPD patients had very severe COPD (GOLD stage IV). Currently, in clinical practice classification of disease severity purely by amount of airflow limitation, as was used to categorise patients in the ECLIPSE study, are often no longer sufficient; also exacerbation history (with hospitalisation) and severity of symptoms are taken into account when categorising patients.

Additionally, the subjects included in the ECLIPSE study were Caucasian and living in North America, Europe, or New Zealand.

From the ECLIPSE study, we have selected subjects that met our inclusion requirements; since we only included subjects with complete availability of all three CT scans, we have only selected the surviving subjects and subjects willing and able to complete the study. The subjects included in our sub-cohort were somewhat younger (61.3±8.0 vs. 62.3±7.9 years old), were less often males (61.1% vs. 62.6%), had lower BMI (25.8±4.5 vs. 26.6±5.5 kg/m^2) and were more often smokers without COPD (19.4% vs 14.2%) as compared to the total ECLIPSE population. The percentage current smokers was higher (42.3% vs. 39.9%) but the mean number of pack years was lower (43.3±24.8 vs. 46.2±27.1) compared to the total ECLIPSE population.

Vertebral fracture diagnosis

In all chapters, vertebral fractures were diagnosed based on the method described by Genant.[3] This method is based on direct quantitative morphometric measurements of vertebral dimensions (height loss) but VF diagnosis is not contingent on vertebral endplate fractures. Other, more recently proposed VF diagnosis strategies are based on morphological (qualitative) criteria such as endplate depression (the Algorithm Based Qualitative (ABQ) method,[31] or a combination of both methods.[32,33]

Morphological vertebral fractures seem to be more strongly associated with lower BMD, incident osteoporotic vertebral and nonvertebral fractures than morphometric vertebral deformities.[34] However, the anatomical spinal distribution of morphometric deformities and morphologic fractures is different. ABQ-diagnosed fractures have a principal peak at the thoracolumbar junction while morphometric fractures have a principal peak in the mid-thorax.[34] This suggests that the difference between the two is more fundamental than simply that of two alternative means of describing the same phenomenon. The main reason for using the Genant classification of VFs in this thesis was based on the fact that inclusion and outcome criteria related to VFs of almost all intervention trials in the field of osteoporosis and fracture prevention during the last 25 years have been using the Genant classification and have been implemented in the Dutch and also international guidelines. The findings with regard to VFs in this thesis can therefore directly be translated to clinical practice.

In this thesis, we only have assessed VFs between T_1 and L_1 because of the nature of our scans and we therefore have no information about prevalence and/or incidence of VFs in the lower lumbar part of the spine. This may have led to an underestimation of VF prevalence and incidence although according to literature, most VFs occur in the mid-thoracic and thoracolumbar region,[12,14,35-38] which are both visible on chest CT scans.

Since we have diagnosed VFs on chest CT scans with morphometry software, this may have resulted in a more sensitive method to assess VFs compared to morphometric or visual assessment of DXA or X-ray images, as reported in many other studies and therefore this could have resulted in a higher proportion of subjects with prevalent or incident VFs in our studies. In addition, in the absence of beam divergence on CT images and with use of morphometry software, small height changes can be detected that could have resulted in higher VF grade, compared to studies performed on X-ray images. This is confirmed in **chapter 2** of this thesis, where morphometric assessment of VFs on chest CT images was most sensitive.

Use of BA as bone density measure

In this thesis, we have measured BA directly from chest CT scans as they are made for pulmonary evaluation. Even though the CT scanners were regularly calibrated using industrial and clinical standards, the use of direct BA measurements for fracture risk estimation is more than once discussed in literature.

A recent systematic review by Gausden et al. reported that direct BA measurements from diagnostic CT scans has the potential to be used for opportunistic screening, and that future research efforts should focus on identifying thresholds at specific anatomic regions in high-risk patients.[39] If these thresholds would be identified, the method could be extremely valuable for orthopaedic surgeons and in primary care.

Shousboe and Ensrud state that the use of low-dose CT (LDCT) could be particularly useful in countries such as China, where there is more access to CT than to DXA.[40] In other countries, where access to DXA is more common, the use of LDCT could still be useful to address osteoporosis diagnosis and treatment gap. Adults aged over 55 with a heavy smoking history are an interesting target audience for opportunistic screening, due to the recommended lung cancer screening using LDCT. The major drawbacks mentioned by Shousboe and Ensrud are the lack of BA measuring software in clinical CT scanners, and clear thresholds at different locations such as L_1 or hip with corresponding specificity and sensitivity. They also point out that incidental findings on CT are not always followed up in primary care due to work-load, so a change in healthcare systems workflow is also necessary.

VF locations and loading

In line with expectations, BA in subjects with prevalent or incident VFs was lower than in subjects without VFs. Interesting was that we also found a difference in BA between subjects with VFs at the most common VF-locations (T_7-T_8 and T_{11}-T_{12}) and subjects with VF at (also) other locations.

From a biomechanical point of view, the bimodal distribution of VFs throughout the spine can be explained partly by loading patterns in the spine: the apex of the curve is usually found in the T_7-T_8 area, while the curvature changes from thoracic kyphosis to lumbar lordosis in the T_{11}-T_{12} area. It is therefore not surprising that these common VF locations endure the highest loadings during daily activities such as bending, twisting while carrying something, lifting weight, or pushing.[29] It makes sense that vertebrae that endure the highest loadings according to computational models can fracture at higher BA than vertebrae that are not as heavily loaded. However, this is something that can be shown indirectly via computational models and fracture data combined with density measurements, but it cannot be directly proven.

The results presented in **chapter 6** are in line with our expectations based on computational models as presented by Bruno et al.,[29] and suggest also other factors than only BA play an important role in the bimodal distribution of VFs.

Coronary artery calcification

Regarding **chapter 7**, there are a few considerations to keep in mind. First of all, Agatston score was only measured at baseline and follow-up data concerning Agatston score was not available. Additionally, we had a limited number of subjects with availability of Agatston score (n=586) and the variation in score was large (ranging from 0 in 196 subjects, up to 4806). Due to the numbers of subjects and the clinical interpretation of Agatston score, we have divided the subjects in three groups; the zero Agatston score group (with 0 Agatston Units (AU)), the

medium Agatston score group (1-400 AU), and the high Agatston score group (>400 AU). The interpretation of the zero and high group is quite straight forward, but there is a room for discussion regarding the clinical interpretation of the medium group.

Opportunistic screening

BA, prevalent VFs, kyphosis angle, and CAC are measures that can directly be derived from the CT images. Both VFs and CAC can be asymptomatic but are potentially important comorbidities, each of which is amenable to effective interventions and therewith an opportunity for improvement in patient care. Interestingly, in the clusters described by Vanfleteren et al.,[41] the cachectic cluster had the highest prevalence of osteoporosis (52%) but a relatively low cardiovascular risk, while the cardiovascular cluster showed the second highest prevalence of osteoporosis (37%). The finding that the presence of VFs and CAC are associated independent of bone density, emphasize that there is a substantial probability that opportunistic evaluation of CT images originally performed for pulmonary evaluation in smokers with or without COPD will lead to detection of other important comorbidities.

As mentioned in the introduction, the prevalence of comorbidities among COPD patients is reported to be very high[42-44] and independent from COPD severity.[45] The findings presented in this thesis are in line with the concept of COPD as a complex multicomponent disease with both pulmonary and extrapulmonary events, and that imaging techniques primarily used for pulmonary evaluation could also be used for detection of extrapulmonary disorders like osteoporosis, CAC and VFs.

Final conclusions

Given the VF prevalence of 21.6% in COPD subjects and the high risk of subsequent VFs in those with a prevalent or incident VF, we propose to systematically evaluate the presence of VFs when these patients have chest X-ray or chest CTs made for pulmonary evaluation. Improvement in patient care can be achieved by increasing awareness among pulmonologists and radiologists about the clinical importance for recognizing VFs. Patients with VFs should be further evaluated and treated according to local osteoporosis and fracture prevention guidelines.

Future perspectives

One of the major areas where profit can be made is full automatization of the detection of BA, VFs, and CAC, since methods used in clinical practice and the methods used for the studies presented in this thesis require human interaction. Software that fully automatic detects BA,

VFs and CAC would mean higher cost efficiency (less time-consuming) and fewer missed cases. Furthermore, such a software program could assess the vertebrae taking the 3D shape into account; the method of Genant determines whether the vertebra is fractured based on 2D images while vertebrae are 3D structures. Such an automated 3D detection of VFs should take height loss of the vertebral body into account as well as deviations in the vertebral endplate, to make sure all information about the 3D shape of the vertebra is considered. Statistical shape models of the vertebrae should be created for comparison.

Additionally to automatization of VF recognition, further research to standardise BA measurements is required; although BA measurements on clinical scans is very promising in research settings,[39] currently there is still discussion going on about interpretation of the HU numbers in clinical settings. Standardised cut-off values such as BMD expressed in standard deviations are essential to be able to identify patients eligible for treatment. Although BA measurements as presented in this thesis are not ready for 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 clinical chest CT scans.

The subjects researched in this thesis were (former) smokers, and the majority of them had COPD. The common belief is that (thoracic) VFs lead to an increase in thoracic kyphosis, which leads to a decrease in pulmonary function. However, there are very few publications in literature addressing this issue. Although we did not find significant differences in prevalence or incidence of VFs between smokers with or without COPD after adjustment for clinical parameters, the potential effect of VFs on pulmonary function is particularly of interest in the latter patient group; in subjects with already impaired respiratory function preventing even further detoriation could be vital.

The COPD patients in our study population might not be a very good reflection of the COPD patients as seen in clinical practice; COPD patients often use oral GCs while this was an exclusion criteria for the ECLIPSE study. It is known that (long-term) use of GCs has negative influence on bone density, and therefore further research in prevalence and incidence of VFs specifically in a group of COPD patients representing the patients as seen in clinical practice is needed. Additionally, since a three-year follow-up is relatively short, long-term results regarding BA, VFs, kyphosis and Agatston score in (former) smokers both with and without COPD would be very valuable.

Apart from offering the technical possibilities, it also is important to increase awareness of fracture risk and improvement in patient care so that a possible new method can be put to good use in clinical practise.

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Chapter 10

Social and scientific impact

Social and scientific impact

In this thesis, we studied the associations between clinical determinants such as age, sex, smoking status, smoking history, bone attenuation (BA) measured on computed tomography images (CT) and thoracic kyphosis with prevalent and incident vertebral fractures (VFs) in smokers with and without chronic obstructive pulmonary disease (COPD). Additionally, we aimed to study the associations between BA and VF location and the association between VFs and coronary artery calcification (CAC) in this specific population. We used data from the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, which is a non-interventional, observational, multicentre study that was initiated to search underlying mechanisms of disease progression in subjects with COPD and to identify biomarkers that may serve as surrogate endpoints and therefore could measure disease progression. In the ECLIPSE study, CT scans of the chest were performed at baseline, one year follow-up, and three year follow-up and the CT images formed the basis for this thesis.

In **chapter 2**, we first studied the reproducibility of three imaging modalities (lateral chest X-ray, chest computed tomography (CCT) and lateral dual-energy X-ray absorptiometry (DXA) images) that are often used in clinical practice to study the level of agreement of these imaging modalities for diagnosis of vertebral deformities from the fourth thoracic to the first lumbar vertebra (T_4 to L_1). We found excellent reproducibility of height measurements of vertebrae with all three imaging modalities and concluded that these imaging techniques could be used for opportunistic screening of vertebral deformities in COPD patients. This finding is of great importance for clinical practice given the importance of diagnosing VFs in subjects of 50 years and older, since the presence of VFs is associated with the risk of vertebral and non-vertebral fractures and higher mortality risk.

In **chapter 3**, we found that one out of four subjects in the ECLIPSE cohort (mean age 61 years, 61% males, 81% with COPD) had a prevalent VF. Additionally we found that a prevalent VF at baseline was a major risk factor for a subsequent VF in the following three years, since 59% of the subjects with a prevalent VF had an incident VF. Based on these findings we propose to systematically evaluate the presence of VFs in patients with COPD who have chest X-rays or chest CTs made for pulmonary evaluation. Improvement in patient care can be achieved by increasing awareness among pulmonologists and radiologists about the clinical importance for recognizing VFs.

In the **chapters 4 to 7**, we found that low bone density (measured by BA) and increased thoracic kyphosis angles were associated with incident VF risk, while for example age and sex were not. We also found an association between CAC and prevalent VFs. Both CAC and VFs can be asymptomatic, but can have more serious medical consequences when left untreated. Additionally, load/strength ratio seems to play a role in VF location within the spine, meaning that certain areas within the thoracic spine are more likely to fracture due to loading patterns in daily life, while fractures in other areas are more likely to be the result of low bone density. The findings in **chapters 4 to 7** attribute to the concept of COPD as a complex multicomponent disease with pulmonary but also extrapulmonary events and comorbidities and that imaging techniques primarily used for pulmonary evaluation could also be used for detection of extrapulmonary disorders like osteoporosis, CAC and VFs.

Based on the findings in this thesis, we strongly believe that opportunistic evaluation of CT images should focus on further automation of detection of low BA, VFs and CAC in patients with COPD. Automated assessment will not only result in more objective assessment, but will also decrease the workload on medical practitioners, and allow for assessment of all pulmonary CT scans at computational costs only, making this extremely suitable for opportunistic screening programs.

The research presented in this thesis is therefore not only relevant to clinicians such as pulmonologists and radiologists, but also for technicians and software developers given the relevance of adequate automated image analysis.

The findings in this thesis have been widely distributed to and recognised by the scientific society. The work of all chapters was presented at international and national conferences and published in peer reviewed international journals including the highest ranked journal in the field of bone research: Journal of Bone and Mineral Research (**chapters 3 and 5**). **Chapter 2** was published in the journal Osteoporosis International in 2018 and was the most frequently downloaded paper from the orthopaedic springer journals in 2018, with 43.000 downloads. The work presented in **chapter 3** was awarded with a young investigator award by the American Society of Bone and Mineral Research in 2017.

Samenvatting

Dit proefschrift richt zich op de klinische implicaties van systematische evaluatie van wervelfracturen op CT (computed tomography) scans van de thorax van (voormalig) rokers met en zonder chronisch obstructieve longziekte (ook wel COPD: chronic obstructive pulmonary disease). De data gepresenteerd in dit proefschrift zijn grotendeels gebaseerd op de ECLIPSE studie. De ECLIPSE (Evaluation of COPD longitudinally to identify predictive surrogate endpoints) studie is een internationaal onderzoek waarin onderliggende mechanismen van COPD ziekteprogressie onderzocht werden, en waarin gezocht werd naar biomarkers waarmee ziekteverloop gemeten kan worden (Clinicaltrials.gov identifier NCT00292552; GlaxoSmithKline study SCO104960). Uniek aan de ECLIPSE studie is dat thoracale CT scans gemaakt werden aan begin van de studie, na één jaar, en na drie jaar, waarbij gebruik gemaakt werd van CT scanners die ook in de klinische praktijk gebruikt worden. Voor dit proefschrift hebben wij systematisch bone attenuation (BA, een mate van botdichtheid) en wervelfracturen (WFs) op thoracale CT scans beoordeeld op baseline, na één jaar en na drie jaar, bij patiënten met en zonder COPD van de ECLIPSE studie. We richtten in ons onderzoek specifiek op associaties tussen klinische kenmerken zoals leeftijd, geslacht, rookstatus en rookgeschiedenis, BA gemeten op CT en thoracale kyfose, en prevalente en incidente wervelfracturen. Daarbij hebben de associaties tussen BA en wervelfractuurlocatie, en de associaties tussen wervelfracturen en kransslagader verkalking (coronary artery calcification: CAC) onderzocht in deze specifieke populatie.

De gouden standaard voor het meten van wervelfracturen is een laterale röntgenfoto van de wervelkolom. Echter, ook laterale DXA (dual-enery X-ray absorptiometrie) scans en CT scans worden in de kliniek gebruikt. In **hoofdstuk 2** hebben we de mate van overeenkomst onderzocht van het diagnosticeren van wervelfracturen van wervels T_4 tot L_1 op DXA en op CT, in vergelijking met de gouden standaard röntgenfoto's. Hiervoor hebben we wervelfracturen beoordeeld met behulp van SpineAnalyzer^{TM} morphometrie software (Optasia Medical, Cheadle, UK) op röntgenfoto's, DXA en CT scans van een groep van 87 patiënten uit het Catharina ziekenhuis in Eindhoven (57% man, 66% met COPD) die deelnamen aan een studie naar osteoporose bij COPD patiënten (NCT01067248).

Na exclusie van wervels met andere deformiteiten werd de methode van Genant et al. toegepast om hoogteverlies in de wervellichamen te meten (hoogteverlies t.o.v. elders in hetzelfde wervellichaam, of t.o.v. de wervels boven of onder de gebroken wervel): graad 1 (mild; 20-25% hoogteverlies), graad 2 (matig; 25-40% hoogteverlies), of graad 3 fracturen (ernstige fracturen; >40% hoogteverlies).

De ICCs (intraclass correlation coefficients, een mate van overeenkomst) voor het meten van hoogte in de wervellichamen waren uitstekend (>0.94) en de Kappa's waren goed tot uitstekend (0.64-0.77). Voor het diagnosticeren van hoogteverlies in het wervellichaam waren de sensitiviteit (51%–73%) en de positief voorspellende waarden (57%–70%) voldoende tot goed voor alle drie de modaliteiten, en de specificiteit en negatief voorspellende waarden waren uitstekend (≥96%). We concludeerden dat thoracale CT en in iets mindere mate laterale

DXA beelden gebruikt zouden kunnen worden voor het screenen op wervelfracturen bij COPD patiënten.

Vervolgens evalueerden wij in **hoofdstuk 3** de prevalentie en éénjarige en driejarige incidentie van wervelfracturen op de thoracale CT beelden van 1239 deelnemers van de ECLIPSE studie (61% man, 81% met COPD). In deze populatie hadden 253 deelnemers (20.5%) tenminste 1 prevalente wervelfractuur, en de cumulatieve incidentie van wervelfracturen was 10.1% binnen één en 24.0% binnen drie jaar na aanvang van de studie. Na statistische correctie voor leeftijd, geslacht, BMI (body mass index), pakjaren (1 pakjaar = 1 pakje per dag gedurende 1 jaar), en rookstatus (voormalig roker of huidig roker), waren prevalentie en incidentie vergelijkbaar tussen rokers en de verschillende COPD GOLD stadia. Opvallend was dat na één jaar 29.2% van de deelnemers met een prevalente wervelfractuur een incidente wervelfractuur had, in vergelijking met 5.1% van de deelnemers zonder prevalente wervelfractuur. Het risico op incidente wervelfracturen binnen één en binnen drie jaar (hazard ratio (HR): 5.1, 95% confidence interval (CI) [3.6-7.4]) en 3.6, 95% CI [2.9-4.6] respectievelijk) was sterk geassocieerd met de aanwezigheid van prevalente wervelfracturen. Daarbij was het risico op incidente wervelfracturen hoger bij meerdere of ernstigere prevalente wervelfracturen, en deelnemers met een incidente wervelfractuur in het eerste jaar van de studie hadden een hoog risico (57%) op incidente fracturen gedurende de twee volgende jaren.

In deze populatie had meer dan de helft van de deelnemers met een prevalente wervelfractuur of met een incidente wervelfractuur in het eerste jaar van de studie, een incidente wervelfractuur tijdens de resterende looptijd van de studie. Dit toont aan dat (voormalig) rokers met of zonder COPD met een prevalente en/of recente wervelfractuur een hoog risico op incidente wervelfracturen hebben.

In **hoofdstuk 4** hebben we de associatie tussen BA en prevalente wervelfracturen gediagnostiseerd op thoracale CT scans en het risico op incidente wervelfracturen onderzocht onder de (voormalig) rokers met en zonder COPD van de ECLIPSE studie. BA was semiautomatisch gemeten in de thoracale wervels T_4 tot T_{12} (waarbij gefractureerde wervels uitgesloten waren van de meting). Hiervoor werd een zelfontwikkelde methode in Matlab gebruikt, en de botdichtheid werd uitgedrukt in Hounsfield Units (HU).

We vonden een significant verschil in BA tussen mensen met en zonder prevalente wervelfractuur (155.6±47.5 HU vs. 162.6±46.2 HU). BA en prevalente wervelfracturen waren significant geassocieerd met incidente wervelfracturen gedurende het eerste jaar en gedurende de volledige looptijd van de studie; leeftijd, geslacht, BMI, rookgeschiedenis, rookstatus en het hebben van COPD waren niet significant geassocieerd met incidente wervelfracturen. Deze resultaten gebaseerd op systemische evaluatie van thoracale CT scans, suggereren dat de combinatie van BA en prevalente wervelfracturen sterk geassocieerd was met het risico op incidente wervelfracturen bij rokers met en zonder COPD op relatief korte termijn.

Het is bekend dat de aanwezigheid van wervelfracturen kan leiden tot een toename van thoracale kyfose: de mate van kromming van het thoracale deel van de wervelkolom. Ook is met behulp van computermodellen uitgerekend dat een grotere kyfosehoek kan leiden tot toename van de belasting van de wervels. De associatie tussen mate van kyfose en incidentie van wervelfracturen is echter grotendeels onbekend. In **hoofdstuk 5** hebben we de associatie tussen prevalente wervelfracturen en mate van kyfose, en de associatie tussen mate van kyfose en incidentie van wervelfracturen bestudeerd in de populatie van 1239 ECLIPSE deelnemers.

Kyfosehoeken werden gemeten van wervel T_4 tot T_9, en van wervel T_4 tot T_{12}. Hoewel de hoeken gemeten werden in liggende positie (op CT beelden), constateerden wij dat de aanwezigheid van wervelfracturen, het aantal wervelfracturen en de ernst van de wervelfracturen geassocieerd waren met de mate van kyfose. De toename van kyfose gedurende het verloop van de studie was klein, maar was significant groter in deelnemers met incidente wervelfracturen. Na statistische correctie voor BA en prevalente wervelfracturen was een grotere kyfosehoek aan het begin van de studie geassocieerd met incidente wervelfracturen binnen één of binnen drie jaar na begin van de studie (HR 1.34, 95% CI [1.12-1.61] en 1.29, 95% CI [1.15-1.45], respectievelijk). Deze bevindingen ondersteunen de theorie dat een grotere kyfosehoek bijdraagt aan grotere belastingen in de wervelkolom.

Naast een grotere kyfosehoek dragen dagelijkse activiteiten zoals buigen, tillen, en draaien bij aan de belasting van de wervelkolom. Uit computermodellen is gebleken dat deze belasting het grootst is in wervels T_7-T_8 en T_{11}-T_{12}, wat zou kunnen wijzen op hoger fractuurrisico in deze wervels. Dit komt overeen met het feit dat de meeste wervelfracturen geobserveerd worden in deze wervels. In **hoofdstuk 6** was onze hypothese dat wervelfracturen op de meest belaste locaties (T_7-T_8 en T_{11}-T_{12}) ontstaan bij hogere BA dan de wervelfracturen op andere locaties in de wervelkolom (T_4-T_6 en T_9-T_{10}). De CT beelden gemaakt bij aanvang van de studie werden gescreend op prevalente wervelfracturen volgens de methode van Genant et al. BA, uitgedrukt in HU werd gemeten in de niet-gefractureerde wervels.

In vergelijking met deelnemers zonder wervelfracturen, hadden deelnemers met prevalente wervelfracturen alleen op de meest voorkomende locaties een significant lagere BA (de groep cWFs, -15%). Deelnemers met wervelfracturen op alleen de overige locaties hadden een nog lager BA (de groep lcWFs, -25%, $p<0.05$ vs. de groep cWFs), en deelnemers met wervelfracturen op zowel meestvoorkomende als overige locaties hadden de laagste BA (-32%, $p<0.0001$ vs. cWFs) ($p<0.0001$ voor alle groepen vergeleken met deelnemers zonder wervelfracturen, $p<0.0001$ voor de trend).

Op elk wervelniveau (T_4 tot en met T_{12}) was een lagere BA geassocieerd met wervelfracturen alleen op de meest voorkomende locaties (OR (odds ratios) tussen 1.5 en 1.9 voor elke 50 HU lagere BA), alleen op de overige locaties (OR tussen 2.2 en 3.4), en zowel op de meest voorkomende als overige locaties (OR tussen 3.8 en 4.6). Deze bevindingen suggereren dat de bijdrage van botdichtheid aan de ratio tussen belasting en sterkte van de wervels verschillend is op verschillende locaties in de wervelkolom, en dat andere factoren naast BA (zoals belasting

gedurende dagelijkse activiteiten of veroorzaakt door bijvoorbeeld een val) de locatie van de wervelfractuur mede bepalen.

In **hoofdstuk 7** hebben we de associatie tussen wervelfracturen (zowel prevalentie als incidentie) en CAC (verkalking van de kransslagaders) onderzocht. Van 586 deelnemers in de ECLIPSE studie (62% man, 70% met COPD) werden de prevalentie van wervelfracturen en de aanwezigheid van CAC. Wervelfracturen werden ingedeeld volgens de methode van Genant et al., en CAC werd uitgedrukt in Agatston score: afwezig, medium (1-400 AU (Agatston Units)), en hoog (>400 AU). Van de deelnemers had 21% een prevalente wervelfractuur, 23% een incidente wervelfractuur, en hadden 196 (33%) een lage, 266 (45%) een medium, en 124 (21%) deelnemers een hoge Agatston score.

Prevalente wervelfracturen waren geassocieerd met medium en hoge Agatston score (OR = 1.83, 95% CI [1.01-3.30] en 3.06, 95% CI [1.45-6.47], respectievelijk). Na correctie voor BA was alleen de associatie met hoge Agatston score significant (OR = 2.47 [1.13–5.40]). Agatston score aan het begin van de studie was niet significant geassocieerd met incidentie van wervelfracturen. Op basis van deze bevindingen concluderen wij dat in de praktijk, (voormalig) rokers met of zonder COPD waarbij wervelfracturen of CAC vastgesteld wordt, ook gescreend zouden moeten worden op CAC dan wel wervelfracturen.

Gezien de hoge prevalentie en incidentie van wervelfracturen bij (voormalig) rokers met en zonder COPD, zouden wij willen voorstellen om CT scans die voor andere medische doeleinden gemaakt worden bij deze patiënten, systematisch te evalueren op aanwezigheid van wervelfracturen. De patiëntenzorg kan verbeterd worden door verbeterde bewustwording van het belang van diagnose van wervelfracturen onder longartsen en radiologen. Patiënten bij wie een wervelfractuur geconstateerd wordt, moeten verder geëvalueerd en behandeld worden volgens de geldende osteoporose en fractuurpreventie richtlijnen.

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♫ *And now, the end is here…*

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Bram, met de wijze woorden van Tina: *You're simply the best* ♫

Curriculum Vitae

Mayke van Dort was born on the 5th of June 1988. Although born in Delft (the Netherlands) she was raised in Arnhem, where she completed secondary school at the Stedelijk Gymnasium Arnhem in 2006. In that same year she moved to Groningen for a bachelor's degree in Life Science & Technology, from which she graduated in 2010. Before taking place in the board of the student association A.S.V. Dizkartes for one year full-time (2009/2010), she participated in a summer school at Trinity College Dublin in the summer of 2009. These two weeks of studying abroad tasted like more, so she decided to apply for the CEMACUBE program, a European double degree Master's programme in Biomedical Engineering.

CEMACUBE was initiated under the Erasmus Mundus Programme 2009-2013 of the European Commission. Mayke was accepted in to the program with support of a scholarship, so she moved to Dublin (Ireland) in 2010 for her first year of the Master's programme. She had the opportunity to finish the full Master's degree at Trinity College Dublin including dissertation thesis over summer (90 ECTS) so received her diploma for Master of Science in Biotechnology from TCD in spring 2012. In September 2011 she moved to Ghent (Belgium) for the second year of the CEMACUBE program (60 ECTS) at the University of Ghent, for which she received the title of International Master of Science in Biomedical Engineering ('burgerlijk ingenieur') in July 2012. After graduation, Mayke took a little break and spent one month teaching English to kids aged 9 to 18 after their regular school hours in Gianyar (Bali, Indonesia).

In 2013, prof. dr. Joop van den Bergh offered her the opportunity to join the academic research group in Maastricht, to study vertebral fractures in the ECLIPSE population, also supervised by prof. dr. Emiel Wouters, and copromotores dr. Lisette Romme and dr. Annemariek Driessen. Highlights during the PhD period were the oral presentation and young investigator award at the yearly conference of the American Society of Bone and Mineral Research in 2017, and being author of the most often downloaded article from the orthopaedic springer journals in 2018, with 43.000 downloads.

After deciding to leave academic research behind, Mayke started an IT traineeship at Sogyo, De Bilt. Currently she is working as a software engineer at Arval, Houten, the Netherlands.

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List of abbreviations

%LAA	percentage low attenuation area
%pred	percentage of the predicted value
95%CI	95% confidence interval
AATD	alpha-1-antritrypsin deficiency
adj. HR	adjusted hazard ratio
AU	Agatston units
AUROC	area under the receiver operating characteristic curve
BA	bone attenuation
BMD	bone mineral density
BMI	body mass index
CAC	coronary artery calcification
CAD	coronary artery disease
CAT	COPD assessment tool
CCT	chest computed tomography
CHD	coronary heart disease
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CVD	cardiovascular disease
cVF	most common vertebral fracture locations
DICOM	digital imaging and communications in medicine
DXA	dual-energy X-ray absorptiometry
ECLIPSE	evaluation of COPD longitudinally to identify predictive surrogate endpoints
FEV_1	forced expiratory volume in 1 second
FFMI	fat free mass index
FVC	forced vital capacity
GC	glucocorticosteroids
GOLD	global initiative for chronic obstructive lung disease
HR	hazard ratio
HU	Hounsfield units
ICC	intraclass correlation coefficient
kV	kilo volts
kVp	peak kilovoltage
lcVF	less common vertebral fracture locations
mMRC score	modified British Medical Research Council score
n.s.	not significant
NCDs	non-communicable diseases
NELSON	Dutch-Belgian lung cancer screening trial
NPV	negative predictive value
OR	odds ratio

PPV	positive predictive value
ROI	region of interest
SD	standard deviation
SDI	spinal deformity index
VF	vertebral fracture
WHO	World Health Organization