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High prevalence of vertebral deformities in COPD patients: relation to disease severity

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Abstract
Bone mineral density decreases with advancing COPD severity, but we do not know whether this is reflected in higher fracture rates. We wished to compare the prevalence of vertebral deformities in COPD patients with those in a population-based reference group, and to determine whether the number of deformities was related to the severity of COPD and how far use of oral corticosteroids (OCS) influenced the prevalence of deformities.
In this cross-sectional study of 465 COPD patients and 462 controls, vertebral deformities were found in 31% of the patients and 18% of the controls ($p<0.0001$). In subjects who had never or sporadically used OCS, deformities were found in 29% of the patients and 17% of the controls ($p<0.0001$). In women the average number of vertebral deformities was almost twofold when COPD severity increased from GOLD II to GOLD III. In men, use of OCS had a small but significant influence.
Prevalence of vertebral deformities was significantly higher in COPD patients than in the controls. In women the average number of deformities was related to COPD severity even after adjustment for other known risk factors. The difference between patients and controls remained significant even in those who never or sporadically used OCS.

Keywords: COPD, prevalence, systemic steroid therapy, vertebral deformities, vertebral fractures

A higher fracture rate caused by osteoporosis may be a significant clinical problem in patients with advanced chronic obstructive pulmonary disease (COPD) [1]. Bone mineral density (BMD) is significantly lower in COPD patients than in healthy individuals, and decreases as the lung disease progresses [2,3]. However, we do not know whether the decrease in BMD is reflected in higher fracture rates.

Many vertebral fractures are never brought to clinical attention [4-7], and valid estimates of the prevalence of these fractures must be based on a radiographic survey of the population. Use of the term "vertebral deformity" is now standard in morphometric studies performed without reference to clinical presentation. In the European Vertebral Osteoporosis Study (EVOS) the mean prevalence of radiographically defined vertebral deformities for the various centres was found to be 12% (by the McCloskey method) for both men and women. There was considerable geographical variation, with the highest rates in the Scandinavian countries. The prevalence increased with age in both sexes, although the gradient was steeper in women [4].

Although a prevalence of vertebral deformities as high as 63% has been reported in COPD patients [1], the relation of COPD to vertebral deformities is difficult to assess in quantitative terms on the basis of previous studies. Prevalence figures vary widely between studies, possibly due to methodological or geographical differences, disease severity and the patients' use of oral corticosteroids (OCS) [1,8]. Furthermore, COPD patients have rarely been compared with healthy controls or with a comparable general population. To our knowledge, there are no studies of the relation between severity of COPD and number of vertebral deformities.

In the present cross-sectional study, our primary aim was to determine the prevalence of vertebral deformities among COPD patients and compare them with a population-based reference group, Secondly, we wished to determine whether the severity of COPD had any impact on the average number of deformities and to what extent the use of OCS influenced the prevalence of deformities.

MATERIAL AND METHODS

The present study is part of a larger study on the consequences of vertebral deformities for lung function. A pilot study of deformities and lung function was performed prior to the main study in 50 consecutively admitted COPD patients in order to calculate the number needed to demonstrate a 12% difference in forced expiratory volume in one second (FEV_1) between patients with and without vertebral deformities. A significance level of 0.05 and a power of 0.80 required the inclusion of 462 COPD patients of both sexes.

Subjects

Glittreklinikken is a rehabilitation centre that provides rehabilitation programmes for patients with pulmonary diseases with varying diagnoses and severity who are referred from all parts of the country. From September 2005 to October 2007, 1004 consecutively admitted COPD patients attending a four-week rehabilitation programme were evaluated for inclusion in the study. Of these, 492 either had to be excluded or did not meet the inclusion criteria. Of the remaining 512, 47 dropped out, resulting in a study group of 465 COPD patients (Fig.1).

Inclusion criteria: patients with COPD in a stable phase whose diagnosis was based on clinical history and lung function values of post-bronchodilator $FEV_1 < 80\%$ and post-bronchodilator $FEV_1/FVC < 70\%$ [9]. A stable phase was defined as no exacerbations involving decreased lung function and need for antibiotics or additional OCS during the previous four weeks. Furthermore we stipulated that the patients' general medical condition should not prevent them from participating in the study.

Exclusion criteria: patients with cancer, inflammatory bowel disease, untreated hyperthyroidism, exacerbation of the lung disease during the previous four weeks, immobility or known kyphoscoliosis from youth.
Written informed consent was obtained from all subjects, and the study was approved by the regional committee for medical research ethics.

Control group

The control group consisted of 462 individuals randomly selected from the Oslo study group in EVOS, which consisted of 587 individuals aged between 50 and 80 years [4]. The prevalence of COPD in this population is not reported, and EVOS did not include lung function tests.

Measurements

Pulmonary function tests were carried out by trained operators in accordance with guidelines laid down by the European Community for Steel and Coal (ECSC) [9] using Master screen equipment (Jaeger GmbH, Würtzburg, Germany). Post-bronchodilator measurements were registered.
The patients were classified into stages II–IV in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [10].
Arterial blood was obtained by a radial artery puncture after 30 minutes' seated rest. The samples were analysed for pH, partial pressures of oxygen (P_aO_2) and carbon dioxide (P_aCO_2) within five minutes of the puncture (Radiometer ABL 725, Copenhagen, Denmark).
Height and weight were measured with the patients wearing light indoor clothing and no shoes, and body mass index (BMI) was calculated in terms of kg/m^2.
Information about smoking and treatment with corticosteroids, calcium and vitamin D, hormone replacement therapy (HRT) and bisphosphonates was obtained from patient interviews and medical records. Smoking exposure was estimated in terms of pack years. Patients were classified as never users or users of OCS. Patients with sporadically OCS use were classified as users if they had ever taken OCS for more than four two-week periods, and we estimated that OCS use for four two-week periods would be comparable to two months' continuous use. In EVOS, subjects were classified as OCS users if they had ever taken OCS daily for a period of two months or longer. In our study, patients taking less than this were classified as never users. Prednisolone was the only type of OCS used, and we estimated the cumulative dose for this drug. For those who only took OCS during exacerbations, we based our estimates on a cumulative dose of 0.3 g prednisolone per exacerbation period [10,11]. The use of inhaled corticosteroids (ICS), bisphosphonates, calcium and vitamin D was recorded in terms of number of years.
Thoracic and lumbar spine radiographs were taken according to a standardized protocol [4], with the patient lying in the left lateral position. For the thoracic radiographs, a breathing technique was used that allowed blurring of the overlying ribs and lung details by motion. The film was centred at Th7 for the thoracic and at L2 for the lumbar radiographs. All radiographs from patients and controls were evaluated at the Center for Muscle and Bone Research, Benjamin Franklin Hospital, Berlin.
A semi-quantitative approach was used to assess vertebral deformities. Anterior (a), mid (m), and posterior (p) heights and corresponding height ratios a/p, m/p, p/p_{up}, p/p_{low} were estimated. Height p_{up} and p_{low} are the posterior heights of the vertebrae one level above and one below the assessed vertebra. A vertebra was considered to have a deformity if any height ratio at baseline was below the threshold of 0.80 [12].
As the original evaluation of the EVOS population was done morphometrically at the Center for Muscle and Bone Research, and as the prevalence of vertebral deformities was obtained by both the Eastell and the McCloskey algorithms, the EVOS images were re-evaluated by the above method to ensure comparability between the COPD and control groups. The re-evaluation was expected to result in different figures for the prevalence of vertebral deformities between the original EVOS evaluation from the Oslo material and the evaluation in the present study.

Because the hospital changed X-ray equipment during the study, 255 of the radiographs were taken with a Diagnost 88 (Paris, France) and the rest with a Swissray ddRFormula Plus (Hochdorf, Switzerland).

Statistics

Categorical variables were analysed by chi-squared tests. Pearson or Spearman correlations were used to estimate the associations between two continuous variables. Differences between two independent groups were tested by two sample t-tests or Mann Whitney tests, as appropriate. Univariate and multivariate Poisson regression models were used to estimate the relative changes in the average number of deformities, with 95 % CI.

To test whether the effect of GOLD stage on the average number of vertebral deformities was the same for both sexes, the interaction term GOLD × sex was tested by a likelihood ratio test. Two-sided p values ≤ 0.05 were considered statistically significant. The analyses were performed with SPSS version 16 (SPSS Inc., Chicago, IL).

The curve for the relative change in the average number of deformities (with 95% CI) to patient age was estimated by generalized additive regression GAM with the LOG link in statistical software R, version 2.6.0 for Windows, R Foundation for Statistical Computing, Vienna, Austria (http://www.R-project.org.).

RESULTS

Sex distribution did not differ significantly between the excluded and included COPD patients, but age and FEV_1 (%) differed slightly but significantly between the two groups (Table 1).

Sex and age did not differ significantly between the study group and the group of dropouts. Lung function tests were not reported for the dropouts.

The study group and the control group had the same distribution with regard to sex, BMI and use of HRT by women. Mean age was two years older in the control group ($p = 0.002$). Significant differences between patients and controls were also found for pack years and use of calcium/vitamin D and OCS. For the control group, bisphosphonates was not available at the time of the EVOS study, and we possessed no data on the use of inhaled corticosteroids or cumulative dose of OCS (Table 2).

Vertebral deformities were found in 143 (31%) of the patients and 82 (18%) of the controls ($p < 0.0001$). In those who had never or only sporadically used OCS, deformities were found in 29% of the patients and 17% of the controls ($p < 0.0001$). In OCS users the difference in prevalence of vertebral deformities between patients and controls was not significant (Fig. 2).

The mean numbers of vertebral deformities were 0.8 in the patients and 0.4 in the controls ($p < 0.0001$) (Table 2). In the 143 patients with deformities, the range of deformities was 1 to 13. The mean numbers of vertebral deformities in patients with GOLD stages II, III and IV respectively were 0.5, 0.7 and 1.1 in men, and 0.6, 1.1 and 0.5 in women (Table 3).

Due to the nonlinear effect of age on the average number of deformities (Fig. 3), patient age was categorized into two groups, above and below the median age (63 years) in the univariate and multivariate Poisson regression models. This resulted in 257 patients ≤ 63 years and 208 patients > 63 years. A highly significant interaction effect was found between sex and GOLD stage ($p < 0.001$). Therefore stratified analyses for sex were performed for the univariate and multivariate Poisson regression models.

In the female patients (Table 4), the average number of vertebral deformities was significantly associated with GOLD stage, age group and current use of HRT, but not with BMI, number of years of ICS use, cumulative OCS dose, use of bisphosphonates or previous use of HRT. Women in GOLD stage III had a 97% higher average number of deformities than women in GOLD stage II ($p < 0.0001$). There was no significant difference in the average number of deformities between GOLD II and IV. For current use of HRT the relative change in the average number of deformities

was 0.42 ($p = 0.020$). Patients over 63 years had a 2.44 ($p < 0.0001$) times higher average number of deformities than the age group below 63 years.
In the male patients (Table 4), the average number of vertebral deformities was significantly associated with cumulative dose of OCS, number of years of ICS use and BMI, but not by GOLD stage, age group or use of bisphosphonates. For every additional gram of cumulative OCS dose the average number of deformities increased by 3% ($p < 0.0001$). Patients using ICS had a reduction of 7% ($p < 0.001$) for every additional year of ICS use. The average number of deformities was reduced by 5% ($p < 0.004$) when the patient's BMI increased by 1 kg/m^2.
The average number of vertebral deformities was not significantly associated with pO_2, pCO_2, pH or pack years in any of the above groups in either the univariate or the multivariate analyses.
In both patients and controls, deformities were more frequent in the mid-thoracic region and at the thoracic–lumbar junction. For all vertebral levels a larger number of patients than controls had deformities (Fig. 4).

DISCUSSION

The prevalence of vertebral deformities was 72% higher in COPD patients than in a general population sample from the same geographical region. The difference remained almost the same when the patients and controls who never or only sporadically used systemic steroids were compared. The use of HRT did not differ significantly between the study and the control group.
Previous studies of vertebral deformities in COPD patients have shown a prevalence range of 27 [13] to 63% [1], both of which are higher than in the general population in EVOS. In two studies that reported a prevalence of over 60%, all the patients had been continuous users of OCS [1,14]. In one of the studies COPD patients who had never used OCS were compared with COPD patients who were continuous users, and the never users had a prevalence of 49% [1]. Neither of the studies had controls without lung disease, and neither contained information about the prevalence of vertebral deformities in the general population in the same geographical region.
In contrast to our findings, two previous studies reported no difference in the prevalence of vertebral fractures between COPD patients and controls [13,15]. However, the first study included men only, and the control group, of 27 healthy men, was small [15]. The second study consisted of 127 COPD patients, and patients admitted to hospital without a diagnosis of COPD or asthma were used as controls [13]. Neither study contained information about the prevalence of vertebral deformities in the general population.
The differences in reported prevalence are not unexpected, as the studies used different methodologies and inclusion and exclusion criteria. Moreover, EVOS revealed a substantial geographical variation in the prevalence of vertebral deformities in Europe, and a similar geographical variation could be expected for COPD patients.
In the present study the average number of vertebral deformities was only significantly associated with the severity of COPD in women. An increase in severity from GOLD stage II to stage III was associated with an almost twofold increase in the average number of vertebral deformities. Adjusting for confounding variables did not substantially change the relationship between GOLD stage and number of deformities. There was an unexpected, but not statistically significant reduction in relative change (RC 0.76) in the average number of deformities with an increase in severity from GOLD II to IV compared with that from GOLD II to III. This result should be interpreted with caution, considering that GOLD IV represent the patients with $FEV_1 < 30\%$ or $FEV_1 < 50\%$ of predicted and chronic respiratory failure. The patients in the lower half of this category can hardly be represented, and probably only a few of the patients in the upper half attend a rehabilitation programme. This is supported by the fact that in our study the number of GOLD IV patients was only half that of GOLD III patients, and the average FEV_1 for GOLD IV is 30% of the predicted, while for GOLD III it is approximately 39%.
In women the average number of vertebral deformities was also significantly associated with age, probably owing to postmenopausal bone loss. Current use of HRT gave a significant reduction of

almost 60% in the average number of vertebral deformities, while previous use of HRT did not. This is in accordance with a Swedish study [16], which showed that recent use of HRT is required for optimal fracture protection.

In men we found no effects of COPD severity on the average number of vertebral deformities. This gender difference may be related to women's generally higher propensity for developing osteoporosis. As BMI increased there was a significant reduction in the average number of vertebral deformities. Although the effect was weak, it is consistent with previously published results [17].

According to a recent review by Yang et al [18], the effect of prolonged ICS use on fracture rates and BMD is not clear. In our study, ICS use was associated with a small but statistically significant reduction in the average number of vertebral deformities for men, but not for women. We also found a small but significantly greater number of vertebral deformities with a rise in cumulative dose of OCS in men, but not in women. We have no ready explanation for this gender difference, but an effect of OCS in the women could possibly have been masked by other factors such as differences in use of bisphosphonates and HRT in this group. However, this is entirely speculative. Our method of recording OCS use was adjusted to the method used in EVOS (see "Measurements"). When the patients and controls who never or only sporadically used systemic steroids were compared, a significant difference was still found between the groups with regard to vertebral deformities. This could indicate that the effect of COPD on vertebral deformities does not depend on OCS use alone.

Our study has several strengths. One is that all the COPD patients admitted during the study period were evaluated for inclusion. Furthermore, by using the GOLD classification we were able to relate vertebral deformities to COPD severity. The patients admitted for rehabilitation may be those with more severe disease, but this was taken into account by the use of GOLD staging. We do not know whether the patients admitted are representative of COPD patients in general in Norway. Patients who apply for rehabilitation may be more motivated to take care of their health than the general population. However, our clinical impressions of patients admitted to the clinic in general are that many of them are smokers, have not participated in physical training for several years prior to admission, and do not seem to know what to expect from a rehabilitation programme. Thus, the external validity is probably sufficient for COPD patients in GOLD stage II and worse. Furthermore, all radiographs from patients and controls were evaluated at a single centre, which excludes between-centre variations in the evaluation of deformities.

On the other hand, the present study was conducted almost 15 years after EVOS. If secular changes have occurred in the prevalence of vertebral deformities in the general population, this could have had consequences for the use of EVOS material as a control group.

The presence of vertebral deformities has been shown to predict subsequent deformities [19,20]. Vertebral deformities may reduce lung function [13,21], cause pain and anxiety and reduce physical capacity [22], and are therefore a burden on the individual and society. Early identification and targeted interventions for the growing number of COPD patients with a high risk of deformities could reduce this burden.

In conclusion, our results show a significantly higher prevalence of vertebral deformities in COPD patients than in a population-based cohort. In women the number of deformities was related to the severity of COPD even when adjustment was made for other known risk factors. The difference between patients and controls remained significant even for individuals who had never or only sporadically used systemic steroids, which suggests that the lung disease itself has a specific effect.

Text to figures

Fig. 1. Flow chart of the patient selection.

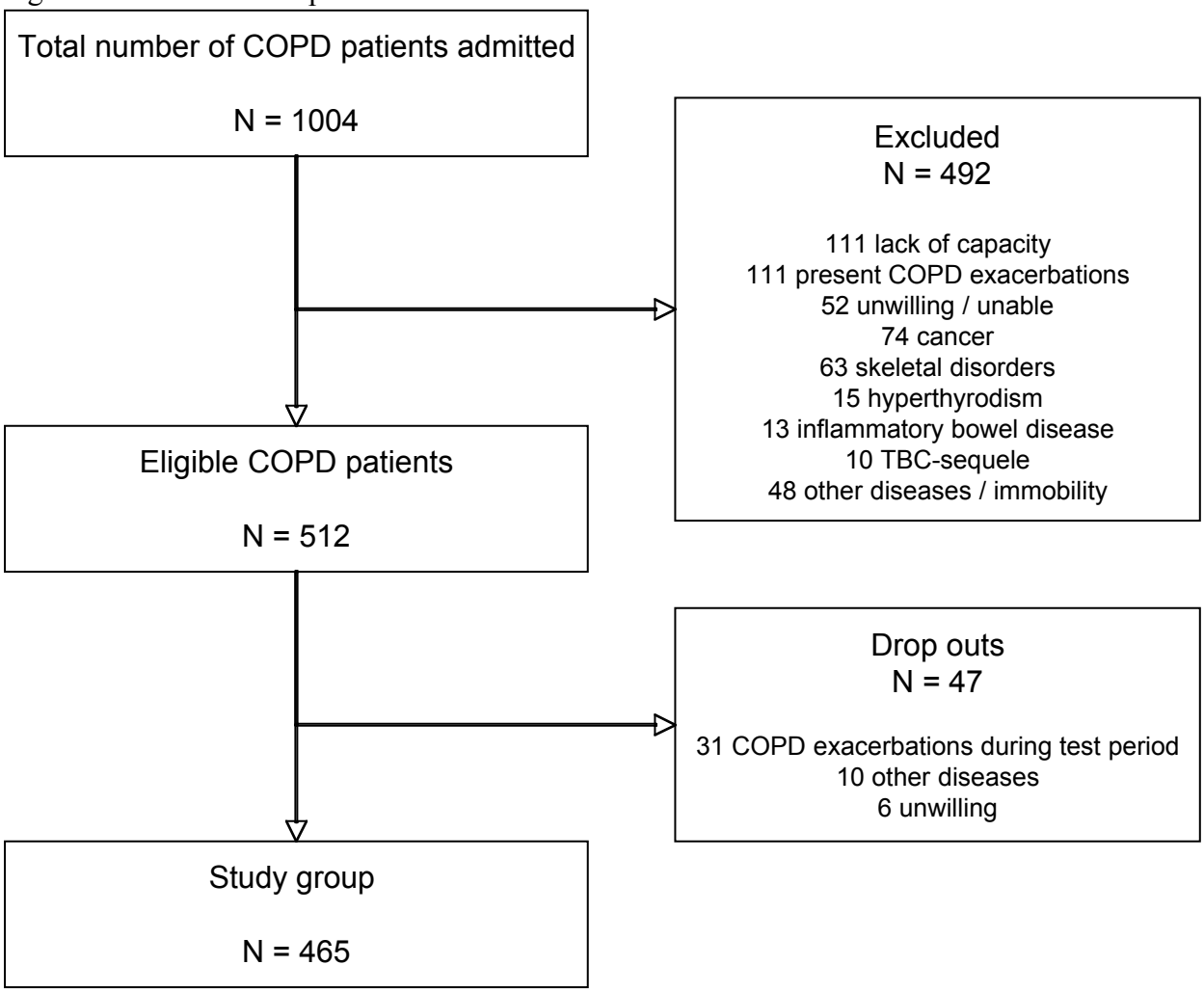


Fig. 2. Vertebral deformities in patients versus controls. Values given as affected persons in per cent of the actual group. “All”: all patients and controls; “Never OCS”: never used oral corticosteroids (OCS) daily for more than two months or sporadically for more than four two-week periods; “OCS”: used OCS daily for more than two months or sporadically for more than four two-week periods; *: $p < 0.0001$

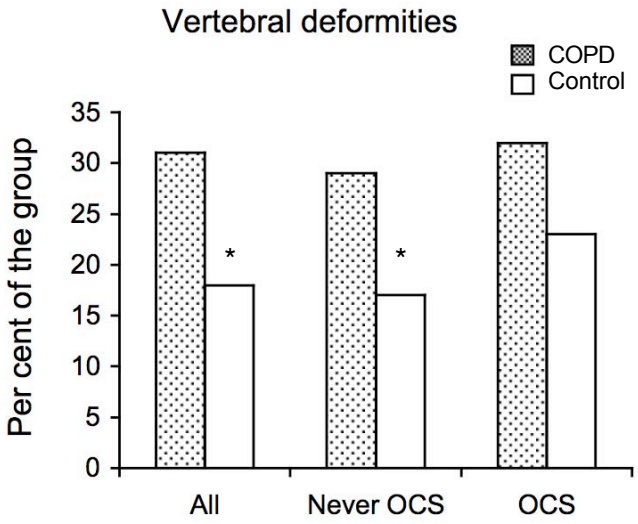


Fig. 3. Estimated relative change in the average number of deformities (solid line) with 95% confidence intervals (dashed line) related to patient age.

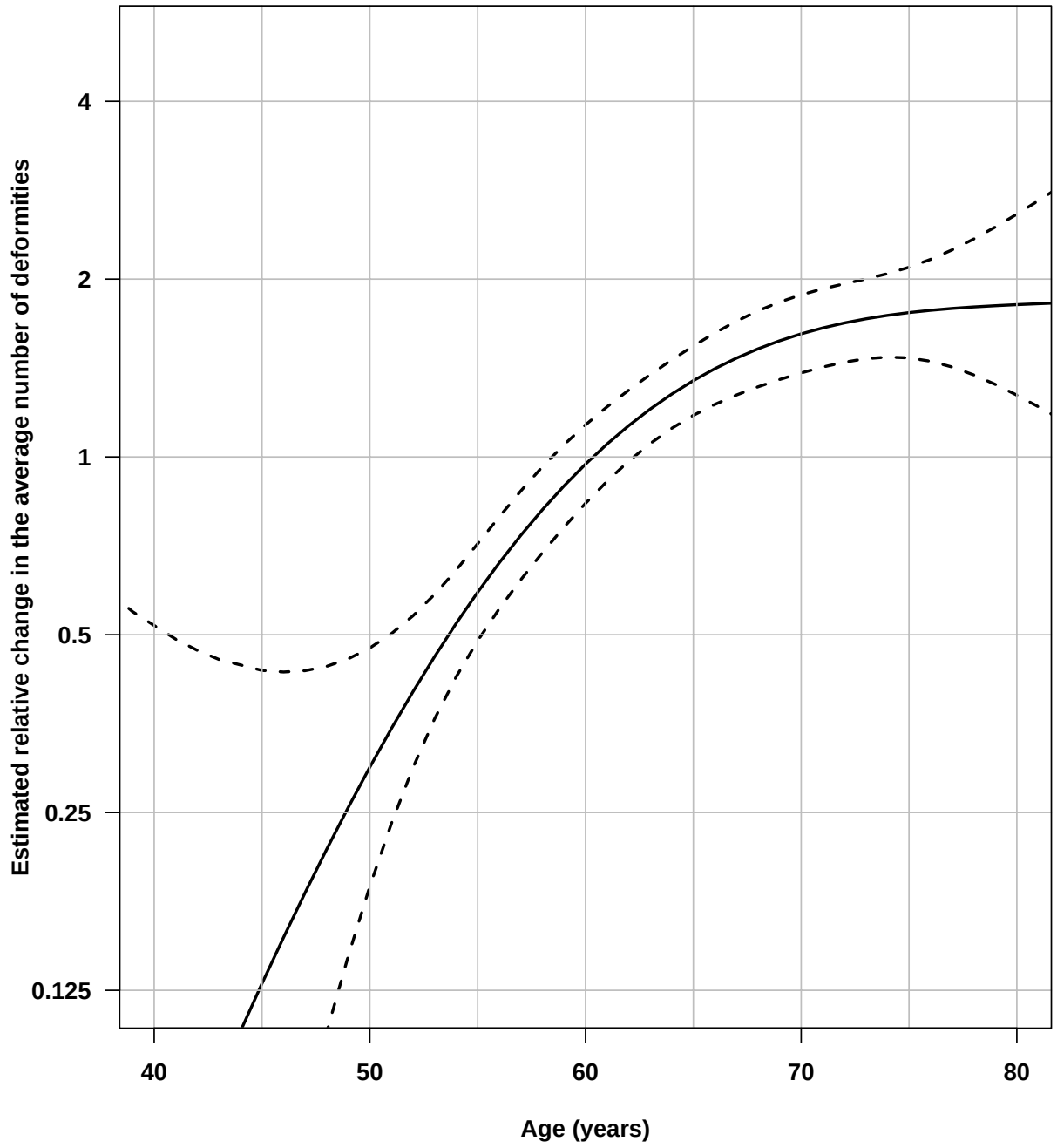
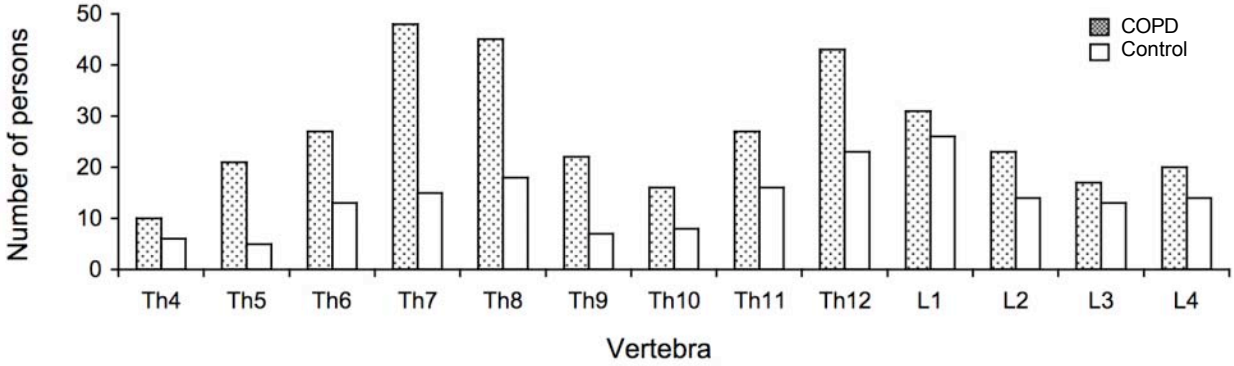


Fig. 4. Number of patients (hatched bars) and controls (open bars) having deformities in vertebrae Th4 – 12 and L1 – 4.


Number of persons
50
40
30
20
10
0
COPD
Control
Th4
Th5
Th6
Th7
Th8
Th9
Th10
Th11
Th12
L1
L2
L3
L4
Vertebra

Tables

Table 1. Excluded versus included COPD patients.

	Excluded n = 492	**Patients included n = 465**	***p***
Men/Women	234 (47) / 259 (53)	231 (50) / 234 (50)	0.514
Age (years)	66 ± 9	63 ± 8	< 0.0001
FEV_1 (% of pred.)	43 ± 15 [a]	45 ± 14	0.020

Values given as number (percent) or mean ± SD

[a] 12 missing values; FEV1: post-bronchodilator forced expiratory volume in one second

Table 2. Subject characteristics for the study and the control group.

	Patients n=465	**Controls** n=462	***p***
Men/Women	231 (50) / 234 (50)	228 (49) / 234 (51)	0.973
Persons with deformities	143 (31)	82 (18)	< 0.0001
Men/Women with deformities	74 (52) / 69 (48)	39 (48) / 43 (52)	0.641
Number of vertebral deformities	0.8 {0.6 – 0.9}	0.4 {0.3 – 0.5}	< 0.0001
Age (years)	63 [32 - 83]	65 [50 - 80]	0.002
BMI (kg/m^2)	25 [14 - 54]	25 [15 - 46]	0.063
Pack years	30 [0 - 114]	10 [0 - 150]	< 0.0001
OCS	201 (43) [a,b]	31 (7) [a]	< 0.0001
Cumulative dose OCS (g)	0.9 [0.0 – 180.0]	-	-
ICS [c]	430 (93)	-	-
HRT [d]	86 (37)	68 (29)	0.157
Calcium-/vitamin D	73 (16)	27 (6)	< 0.0001
Bisphosphonate	44 (10)	0	-

Values given as number (percent), mean {95%CI} or median [range]; [a] Number (percent) of persons who have used oral corticosteroids (OCS) daily for more than two months or [b] sporadically use for more than four periods of two weeks; [c] Number (percent) of patients who have used inhaled corticosteroids (ICS); [d] Number of women (percent of women in the group) who currently or previously have used hormone replacement therapy (HRT).

Table 3. Subject characteristics for men and women in the study group.

	Men n=231	**Women** n=234	**p**
GOLD II	73 (32)	92 (39)	
GOLD III	114 (49)	98 (42)	0.195
GOLD IV	44 (19)	44 (19)	
Age (years)	63 [42 - 83]	63 [32 - 81]	0.694
BMI (kg/m^2)	26 [16 - 46]	24 [14 - 54]	0.002
Cumulative dose OCS (g)	0.6 [0.0 – 74.2]	1.2 [0.0 – 180.0]	< 0.0001
Years used ICS	6 [0 – 25]	5 [0-25]	0.804
Bisphosphonate use	22 (10)	22 (9)	0.964

Values given as number (percent) or median [range].

GOLD: severity of lung disease in 3 categories (II - IV); BMI: body mass index; OCS: oral corticosteroids; ICS: inhaled corticosteroids

Table 4. Relative change of average number of vertebral deformities related to risk factors for osteoporosis. Univariate and multivariate Poisson regression analyses were performed separately for men and women.

	Unadjusted RC (relative change) {95%CI}	**p**	**Adjusted RC** (relative change) {95%CI}	**p**
Men				
GOLD III [a]	1.23 {0.76 – 1.99}	0.398	1.18 {0.79 – 1.77}	0.413
GOLD IV [a]	1.69 {0.92 – 3.12}	0.093	1.51 {0.95 – 2.41}	0.084
BMI	0.97 {0.93 – 1.01}	0.132	0.95 {0.92– 0.98}	0.004
ICS [b]	0.96 {0.92 – 1.00}	0.038	0.93 {0.90 – 0.97}	< 0.0001
Cumulative OCS[c]	1.02 {1.01 – 1.03}	0.001	1.03 {1.01 – 1.05}	< 0.0001
Bisphosphonates	0.78 {0.38 – 1.61}	0.504	0.70 {0.38 – 1.29}	0.251
Age > 63 [d]	1.24 {0.81 – 1.90}	0.323	1.28 {0.94 – 1.75}	0.123
Women				
GOLD III [a]	1.64 {0.96 – 2.78}	0.068	1.97 {1.42 – 2.73}	< 0.0001
GOLD IV [a]	0.84 {0.43 – 1.64}	0.606	0.76 {0.45 – 1.28}	0.301
BMI	1.00 {0.96 – 1.04}	0.809	1.00 {0.98 – 1.03}	0.833
ICS [b]	0.99 {0.94 – 1.03}	0.537	0.98 {0.95 – 1.01}	0.257
Cumulative OCS[c]	1.01 {1.00 – 1.01}	0.111	1.00 {0.99 – 1.01}	0.835
Bisphosphonates	0.87 {0.38 – 2.00}	0.750	0.70 {0.41 – 1.19}	0.184
Age > 63 [d]	2.02 {1.26 – 3.25}	0.004	2.44 {1.78 – 3.33}	< 0.0001
HRT currently [e]	0.57 {0.26 – 1.24}	0.157	0.42 {0.20 – 0.87}	0.020
HRT previously [e]	0.98 {0.56 – 1.72}	0.940	0.97 {0.70 – 1.36}	0.873

GOLD: severity of lung disease in 3 categories (II - IV); BMI: body mass index;
[a] Compared to GOLD II; [b] Number of years used inhalation steroids (ICS); [c] Cumulative dose of oral corticosteroids (OCS); [d] Compared to age ≤ 63; Bisphosphonates: Bisphosphonate use or not; [e] Compared to hormone replacement therapy (HRT) never.

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