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SHORT COMMUNICATION

Is lung function associated with bone mineral density? Results from the Hertfordshire Cohort Study

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Abstract
Summary Given limited information available regarding associations between lung function and bone mineral density among healthy subjects, we undertook these analyses in the Hertfordshire Cohort Study. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC were not associated with bone mineral density at any site; associations with bone mineral content were removed by adjustment for body size.
Purpose There is limited information available regarding the association between lung function and bone mineral density among healthy elderly subjects. We addressed this issue in the Hertfordshire Cohort Study.
Methods From the above cohort, 985 subjects (496 men and 489 women) aged 60–72 years were recruited. All subjects underwent bone density measurements using dual energy X-ray absorptiometry and lung function tests using standardised spirometry. Chronic obstructive pulmonary disease (COPD) was defined as a FEV_1/FVC ratio <lower limit of normal, calculated using separate equations for men and women.
Results Measures of lung function (FEV_1, FVC and FEV_1/FVC) were not associated with bone mineral density at the lumbar spine, femoral neck and total hip in men or women; associations with bone mineral content and bone area were removed by adjustment for body size and lifestyle confounders. In this cohort, there were no associations observed between COPD and any measure of bone mass.
Conclusions There was no association between lung function and bone mass in this community dwelling cohort after adjustment for body size and other confounders.

Keywords Bone disease · Chronic bronchitis · Epidemiology · Osteoporosis · Spirometry

Introduction

Several studies have shown graded relationships between respiratory disease and osteoporosis i.e. the prevalence of reduced bone density and vertebral fractures in patients with chronic obstructive pulmonary disease (COPD) is high [1–4]; furthermore, case–control studies have confirmed reduced bone mineral density (BMD) in COPD patients compared with controls [5, 6], even in those with milder disease [7], while in patients who have osteoporosis and spinal deformities, reduced pulmonary function is related to the severity of osteoporosis [8–10] in the same way that the worse the level of lung function in COPD patients, the greater the likelihood of low BMD [11].

However, few studies have examined whether the reported association between lung function and BMD is only seen in patients with chronic respiratory disease or

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whether it occurs across the range of lung function observed in the general population. Two previous studies have suggested an association between forced expiratory volume in 1 s (FEV_1) and BMD in both men and women [12, 13]; by contrast, a large study in the USA reported that only moderate to severe airflow obstruction, but not mild airflow obstruction, was associated with an increased risk of osteoporosis, after controlling for age, body mass index and recent use of corticosteroids [14]. Since it is possible that an apparent association between lung function and BMD might be confounded by other factors such as physical activity, we undertook this study to investigate and adjust for the effect of possible confounding lifestyle factors in the relationship between lung function and BMD.

Methods

Study population

The Hertfordshire Cohort Study has been described previously [15]. From 1911 to 1948, midwives recorded information on birth weight and weight at 1 year on infants born in the county of Hertfordshire, UK. The records for people born between 1931 and 1939 have been used in a series of studies linking early growth to health in later life. A total of 3,822 men and 3,284 women born between 1931 and 1939 in Hertfordshire, and still living there, were traced through the National Health Service Central Registry. Permission to contact 3,126 (82 %) men and 2,973 (91 %) women was obtained from their general practitioners. Between 1998 and 2004, 1,684 (54 %) men and 1,541 (52 %) women aged 60–73 years took part in a nurse-administered home interview. Social history comprised own current or most recent full-time occupation or husband's current or most recent full-time occupation for ever married women. Medical history included smoking habit; alcohol intake; physical activity; and details of all currently prescribed medications, coded to the British National Formulary. A total of 1,579 (94 %) men and 1,418 (92 %) women subsequently attended a clinic for investigations. Height was measured to the nearest 0.1 cm using a Harpenden pocket stadiometer (Chasmors Ltd., London, UK) and weight to the nearest 0.1 kg on a SECA floor scale (Chasmors Ltd.).

Nine hundred and ninety six subjects (498 men and 498 women) underwent dual energy X-ray absorptiometry (DXA) to measure their bone mineral density at the lumbar spine and proximal femur (neck, total, intertrochanteric and trochanteric regions), using a Hologic QDR 4500 instrument. Measurement precision error, expressed as coefficient of variation, was 1.55 % for lumbar spine BMD, 1.45 % for total femur and 1.83 % for femoral neck BMD; these figures were obtained by 25 volunteers who were not part of the study undergoing two scans on the same day, getting on and off the table between examinations. Short-term (2 month) precision error for the QDR 4500 was less than 1 % for both sites. Individuals taking drugs known to alter bone metabolism (including oral corticosteroids and bisphosphonates) were excluded from this evaluation, although women taking hormone replacement therapy (HRT) were allowed to participate.

Lung function was measured in 986 of these subjects (496 men and 490 women) using a Micro Spirometer (Micro Medical Ltd.) in the seated position without nose clips. After at least one practice blow, three FEV_1 and forced vital capacity (FVC) readings were recorded. The highest FEV_1 and FVC values from satisfactory manoeuvres were used in the analyses, which did not necessarily come from the same blow. For FEV_1, 84.7 % of the men and 92.2 % of the women had a difference of ≤0.15 l between their two highest readings; for FVC, the corresponding figures were 81.0 % for men and 89.7 % for women. COPD was defined as a FEV_1/FVC ratio<lower limit of normal (calculated using separate equations for men and women [16]). No bronchodilator was given before spirometry was performed. One woman was excluded from this study as she took oral steroids.

The East and North Hertfordshire Ethical Committees granted ethical permission for the study. All participants gave written informed consent.

Statistical analysis

Statistical analysis was conducted using STATA version 11.2. Associations between DXA measurements and lung function were explored using regression analysis techniques, both with and without adjustment for confounders. The confounders considered were age (at DXA), height, body mass index (BMI), exposure to other person's tobacco smoke in the home, smoker status, pack years smoked, alcohol consumption, physical activity (derived from frequency of gardening, housework, climbing stairs and carrying loads), dietary calcium intake, social class, use of inhaled steroids and years since menopause and HRT use in women.

Results

Characteristics of subjects

Table 1 shows the characteristics of the subjects included in the study. Mean ages (standard deviation) were 64.8 (2.5) and 66.4 (2.5) years, in men and women, respectively. None of the subjects were on oral glucocorticoids but 22 men and 36 women were taking inhaled glucocorticoids at the time of

Table 1 Summary characteristics of the cohort

		Men (n=496)		Women (n=489)	
		Mean	SD	Mean	SD
Age (years)		64.8	2.5	66.4	2.5
Height (cm)		174.2	6.8	161	5.9
BMI (kg/m^2)[a]		26.6	1.1	26.9	1.2
Physical activity score		64.0	14.8	61.3	15.0
Dietary calcium intake (mg/day)[a]		1217	1.3	1086	1.3
		Median	IQR	Median	IQR
Alcohol consumption (units/week)		9.1	2.5–21.6	1.5	0.0–5.0
Pack years smoked (amongst current and ex-smokers)		25	12–41	12	4–24
		N	%	*N*	%
Smoker status					
Never		167	33.7	305	62.5
Ex		256	51.6	137	28.1
Current		73	14.7	46	9.4
Exposed to tobacco smoke at home		68	13.9	62	12.9
Taking inhaled steroids		22	4.4	36	7.4
Social class					
I–IIINM		193	41.2	195	39.9
IIIM–V		275	58.8	294	60.1
Years since menopause					
<5 years				13	2.7
–10 years				50	10.3
–15 years				135	27.7
–20 years				100	20.5
>=20 years				71	14.6
Hysterectomy				118	24.2
HRT use					
Never				286	58.6
5 years + ago				89	18.2
Within last 5 years				31	6.4
Current				82	16.8
		Mean	SD	Mean	SD
Bone density					
Lumbar spine	area (cm^2)	71.5	6.5	59.0	5.9
	BMC (g)	77.4	15.6	57.0	13.0
	BMD (g/cm^2)	1.08	0.16	0.96	0.17
Femoral neck	area (cm^2)	5.88	0.36	5.13	0.36
	BMC (g)	5.00	0.80	3.88	0.67
	BMD (g/cm^2)	0.85	0.12	0.76	0.12
Total hip	area (cm^2)	46.5	4.3	36.2	3.4
	BMC (g)	48.4	8.1	32.5	5.8
	BMD (g/cm^2)	1.04	0.13	0.90	0.13
Lung function					
FEV_1 (l)		2.88	0.59	2.01	0.40
FVC (l)		4.04	0.72	2.73	0.47
FEV_1/FVC		0.71	0.08	0.74	0.08
		N	%	*N*	%
COPD[b]		104	21.0	60	12.3

[a]Geometric mean (SD). Data were missing on smoking status for 1 woman; on exposure to tobacco smoke in the home for seven men and seven women; on social class for 28 men; on years since menopause for two women and on HRT use for one woman

[b]Defined as a FEV_1/FVC < lower limit of normal

study. Thirty-four percent of the men and 63 percent of the women had never smoked, while the remainder were either smoking currently (14.7 % men, 9.4 % women) or had smoked in the past (51.6 % men, 28.1 % women). Eighty-two women were taking HRT at the time of study. One hundred and four men and 60 women had COPD. Men had significantly higher ($p<0.001$) BMD and lung function values than women.

Relationships between bone mass at the lumbar spine and total femur with lung function (FEV_1, FVC and FEV_1/FVC ratio) are shown in Table 2. While associations were demonstrated between bone area and bone mineral content (BMC) with FEV_1 and FVC, adjustment for anthropometric and lifestyle factors (age, height and BMI, exposure to other person's tobacco smoke in the home, smoker status, pack years smoked, alcohol consumption, physical activity, dietary calcium intake, social class, use of inhaled steroids, years since menopause and HRT use in women) removed these associations; the effect of body size predominated. FEV_1/FVC ratio showed weaker associations with bone area and BMC. There were no significant associations between any lung function measure and lumbar spine, femoral neck or total hip BMD in men or women, except for a weak association between total hip BMD and FEV_1/FVC ratio in men that was removed by adjustment for body size and relevant lifestyle confounders (Table 3). There were also no associations observed between COPD and any measure of bone mass (bone area, BMC or BMD) in this cohort of healthy free-living elderly adults before or after adjustment for confounders. When we performed analyses having excluded subjects with a diagnosis of COPD according to our definition, our results were little changed. Results at the femoral neck were very similar to those observed at the total femur region.

Discussion

This population-based study explored the association between lung function and bone mass at the lumbar spine, and proximal femur, among 496 men and 489 women aged 60–72 years, participating in the Hertfordshire Cohort Study. This lack of association between measures of lung function and bone mass in a generally healthy population after adjustment for body size and lifestyle confounders contrasts with the relationship observed between bone density and lung function in individuals with lung disease, many of whom require corticosteroid therapy.

COPD and bronchial asthma are risk factors for osteoporosis; these patients often display a loss of significant amounts of both cortical and trabecular bone [1–8, 17]. These patients are also often treated with oral or inhaled glucocorticoids, and this contributes to significant additional bone loss. Apart from glucocorticoids, other factors such as low BMI, reduced muscle mass, reduced physical activity, poor nutrition, smoking and alcohol consumption may also play a crucial role in the causation of poor bone health in patients with impaired lung function. The mechanisms involved in bone loss in untreated patients with chronic reparatory diseases are unknown, but raised levels of inflammatory markers, respiratory acidosis and hypercapnia could play a role. Airway inflammation in COPD and bronchial asthma cause an increase in serum concentrations of

Table 2 Univariate relationships between measures of bone mineral and lung function among participants from the Hertfordshire Cohort Study, displayed as regression coefficients with 95 % confidence intervals and significance levels

	Men			Women		
	FEV_1	FVC	FEV_1/FVC	FEV_1	FVC	FEV_1/FVC
Lumbar spine						
Bone area	2.51 (1.56–3.47), $p<0.001$	2.71 (1.95–3.47), $p<0.001$	−5.70 (−12.9, 1.50) $p=0.12$	3.11 (1.79–4.44), $p<0.001$	3.51 (2.42–4.61), $p<0.001$	−4.47 (−11.5, 2.52) $p=0.210$
BMC	2.48 (0.14–4.83), $p=0.038$	2.69 (0.79–4.60), $p=0.006$	−5.44 (22.7, 11.9) $p=0.54$	4.46 (1.48–7.43), $p=0.003$	4.45 (1.96–6.94), $p<0.001$	−1.30 (−16.8, 14.2) $p=0.87$
BMD	−0.004 (−.03–.02), $p=0.73$	−0.004 (−0.02–0.02), $p=0.70$	0.002 (−0.17, 0.18) $p=0.98$	0.02 (−0.02–0.06), $p=0.24$	0.02 (−0.02–0.05), $p=0.30$	0.042 (−0.16, 0.24) $p=0.68$
Total femur						
Bone area	1.82 (1.19–2.46), $p<0.001$	2.04 (1.54–2.54), $p<0.001$	−4.41 (−9.20, 0.39) $p=0.07$	1.48 (0.74–2.23), $p<0.001$	1.53 (0.91–2.15), $p<0.001$	−1.64 (−5.56, 2.28) $p=0.41$
BMC	2.51 (1.30–3.71), $p<0.001$	2.22 (1.24–3.19), $p<0.001$	2.92 (−6.06, 11.9) $p=0.52$	2.00 (0.72–3.28), $p=0.002$	1.75 (0.68–2.83), $p=0.001$	0.22 (−6.50, 6.94) $p=0.95$
BMD	0.01 (−0.01–0.03), $p=0.19$	0.002 (−0.01–0.02), $p=0.81$	0.17 (0.02, 0.31) $p=0.03$	0.02 (−0.01–0.05), $p=0.27$	0.01 (−0.02–0.04), $p=0.43$	0.037 (−0.12, 0.19) $p=0.64$

Table 3 Multivariate relationships between measures of bone mineral and lung function among participants from the Hertfordshire Cohort Study, displayed as regression coefficients with 95 % confidence intervals and significance levels, after adjustment for confounding variables (age, BMI and smoking status)

	Men			Women		
	FEV_1	FVC	FEV_1/FVC	FEV_1	FVC	FEV_1/FVC
Lumbar spine						
Bone area	−0.14 (−1.01, −0.73), p=0.75	−0.13 (−0.89, −0.64) p=0.74	−0.82 (−6.79, −5.07), p=0.79	−0.10 (−1.29, −1.10), p=0.88	−0.001 (−1.07, −1.07), p=1.00	−0.36 (−1.04, −5.31), p=0.90
BMC	−1.68 (−4, −0.65), p=0.16	−1.55 (−3.63, −0.53), p=0.15	−4.36 (−20.15, −11.42), p=0.59	1.30 (−1.53, −4.14), p=0.37	1.32 (−1.22, −3.86), p=0.31	1.69 (−11.96, −15.32), p=0.81
BMD	−0.14 (−1.01, −0.73), p=0.75	−0.02 (−0.04, −0.0008), p=0.06	−0.05 (−0.22, −0.11), p=0.54	0.02 (−0.02, 0.06), p=0.26	0.02 (−0.01, −0.05), p=0.24	0.03(−0.15, −0.21), p=0.74
Total femur						
Bone area	0.33 (−0.26, −0.93), p=0.27	0.53 (0.01, −1.05), p=0.05	−0.98 (−5.04, −3.08), p=0.64	0.36 (−0.32, −1.04), p=0.30	0.17 (−0.44, −0.77), p=0.59	1.59 (−1.67, −4.84), p=0.34
BMC	0.72 (−0.41, −1.85), p=0.21	0.75 (−0.26, −1.76), p=0.15	1.90 (−5.71, −9.52), p=0.62	0.84 (−0.32, −2.00), p=0.15	0.65 (−0.37, −1.68), p=0.21	1.32 (−4.23, −6.87), p=0.64
BMD	0.01 (−0.01, −0.03), p=0.27	0.01 (−0.01, −0.02), p=0.55	0.08 (−0.05, −0.22), p=0.22	0.01 (−0.02, −0.04), p=0.51	0.01 (−0.01, −0.04), p=0.42	−0.01 (−0.15, −0.12), p=0.83

proinflammatory cytokines, and many of these cytokines are potent stimulators of bone resorption [18–20].

However, the literature is less clear whether lung function across normal values in community-based populations might be associated with BMD. Lekamwasam et al. reported positive associations between FEV_1 and BMD in both men and women in a community-based population in the UK [12]. In these studies, the magnitude of the association seen between respiratory function and BMD in men was weaker than that seen in women; this group studied BMD only at the hip and not at the femoral neck and spine, while only FEV_1 was studied as a parameter of lung function. In these studies, it was hypothesised that possible factors for this association are cigarette smoking, hypoxia, chronic hypovitaminosis due to poor nutrition, limited sun exposure and low levels of physical activity. It is possible that our population studied was generally healthier than the cohort studied by Lekamwasam, and this might explain the lack of association seen in our own study. In particular, we have previously reported a null association between vitamin D levels and lung function in this group [20]. It is also possible that differences may exist in level of water hardness or fluoride concentration between the two counties, although it is difficult to corroborate this.

Our study does have some limitations. Whilst we defined COPD spirometrically, this was not based on post-bronchodilator spirometry, so that a small minority of individuals classified as having COPD by our definition may have had asthma. We undertook measurements of bone mineral using DXA, an assessment method that depends to some degree on body size. Measurement errors are widespread in both the assessments of BMD and lung function that we adopted. Given that measurement error of lung function is likely to be random with respect to BMD, this would tend to lead to an underestimation of any association, and it is therefore possible that we were not able to detect weak associations which may be present.

A study by Sin and colleagues used cut-offs of mild obstruction (FEV_1 ≥80 % of predicted), moderate obstruction (FEV_1 50–80 % predicted) and severe (<50 % of predicted) in a very large study of more than 9,000 participants from the National Health and Nutrition Examination Survey database. While overall airflow obstruction was associated with an increased risk of osteoporosis, these relationships were not apparent in the mildest category of airflow obstruction, and a graded relationship was seen. In our own cohort, only 49 (9.9 %) men and 49 (10.0 %) women had moderate obstruction and even fewer (10 (2.0 %) men and 5 (1.0 %) women) had severe obstruction using these cut-offs. Hence, our results are in accord with this study, and suggest that individuals with mild COPD are not at particular risk of osteoporosis. It is highly likely that case mix is responsible for the divergent literature with population surveys reporting a weaker association than is observed in hospital-based cohorts, where more severe cases may predominate.

In conclusion, we have found no relation between lung function and bone mass after adjustment for body size and other lifestyle confounders in a population-based cohort of men and women in their seventh decade unselected for respiratory disease. These findings contrast with studies of patients who have pre-existing severe COPD and who often require oral glucocorticoid therapy; they suggest that patients with only mild COPD are not at excessive risk of osteoporosis.

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Conflicts of interest None.

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