PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 612–619
Published online 25 September 2006 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1318

ORIGINAL REPORT

Use of beta-2 agonists and risk of hip/femur fracture: a population-based case-control study†

Frank de Vries Pharm D[1], Sander Pouwels BSc[1], Madelon Bracke PhD[1,2], Hubert G.M. Leufkens PhD[1], Cyrus Cooper MA, DM, FRCP, FMedSci[3], Jan-Willem J. Lammers MD, PhD[2] and Tjeerd-Pieter van Staa MD, PhD[1,3]*

[1]*Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands*
[2]*Department of Pulmonary Diseases, Utrecht Medical Center, Utrecht University, The Netherlands*
[3]*MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, United Kingdom*

SUMMARY

Introduction Administration of beta-2 agonists decreased bone mineral density in rats. But the association between bronchodilators and fracture risk has not been studied in humans.
Objectives To examine the association between use of beta-2 agonists and risk of hip/femur fracture.
Methods We conducted a population-based case-control study (6763 cases) in the Dutch PHARMO database. Current beta-2 agonist use was compared to never use. We adjusted for severity of the underlying respiratory disease and disease and drug history.
Results A hospitalisation for asthma/COPD in the year before index date increased risk of hip/femur fracture: crude OR 2.17 (95% CI, 1.41–3.34). Patients using higher doses of beta-2 agonists had increased risk of hip/femur fracture: crude OR 1.94 (95% CI, 1.41–2.66) for daily dosages of $\geq$1600 μg albuterol equivalent. The excess fracture risk reduced after adjustment for disease severity (1.46; 95% CI, 1.02–2.08) and after exclusion of oral glucocorticoid users (1.31; 95% CI, 0.80–2.15). Risk of hip/femur fracture was similar between users of beta-2 agonists, inhaled glucocorticoids and anticholinergics.
Conclusion We found increases in the risk of hip/femur fracture in patients using higher doses of beta-2 agonists. However, the excess risk of hip/femur fracture substantially reduced after exclusion of oral glucocorticoid users and after adjustment for the underlying disease. Risk of hip/femur fracture was similar between users of beta-2 agonists, inhaled glucocorticoids and anticholinergics. The severity of the underlying disease, rather than the use of beta-2 agonists, may play an important role in the aetiology of hip/femur fractures in patients using beta-2 agonists. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — adrenergic beta-agonists; femoral fractures; anti-inflammatory agents; lung diseases obstructive; epidemiologic factors

Received 26 June 2006; Revised 25 July 2006; Accepted 26 July 2006

INTRODUCTION

Beta-2 agonists are drugs that are frequently used in the treatment of asthma and chronic obstructive pulmonary disease (COPD). They have been designed to act on the beta-2 adrenergic receptor, causing smooth muscle relaxation resulting in dilation of bronchial passages. Beta-2 adrenergic receptors are also present at osteoblasts and can modulate bone remodeling.[1] Noradrenergic activation of the beta-2 receptor leads to production of RANK ligand by

* Correspondence to: T.-P. van Staa, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands. E-mail: t.p.vanstaa@pharm.uu.nl
† None to be declared.

osteoblasts. RANK ligand stimulates the formation of osteoclasts, which ultimately leads to a decrease of bone mineral density.[2] Administration of beta-2 agonists decreased bone mineral density and strength in rats,[3] whereas the beta-blocker propranolol had opposite effects.[4]

Orally administered beta-blockers have been associated in epidemiological studies with increased bone mineral density and decreased risk of fracture.[5–7] Given these findings, it would be of interest to establish whether beta-2 agonists would have bone effects opposite to beta-blockers. Systemic cardiac effects and increases in plasma levels have been reported with inhalation of beta-2 agonists.[8–10] A large population-based cohort study found an increased risk of fracture in patients using bronchodilators, but this study did not evaluate in detail the association between type of bronchodilator and risk of fracture.[11] Therefore, the aim of this study was to examine the association between use of beta-2 agonists and risk of hip/femur fracture.

METHODS

Study design

PHARMO-RLS (www.pharmo.nl) is a database that contains the pharmacy dispensing data for a population of about 1 million Dutch patients. These prescription data are linked to a nation-wide hospital discharge register.[12] In the Netherlands, pharmacies maintain a virtually complete register of dispensed medications, which have been prescribed by specialists and general practitioners. Patients are included irrespective of their health insurance or socioeconomic status, and represent about 7% of the general population. Several independent validation studies have shown that the PHARMO-RLS database has a high level of completeness and validity.[12,13] Privacy and confidentiality of individuals is maintained during data collection and complies with the Dutch Data Protection Act.

Cases and control subjects

Within PHARMO-RLS, a case-control study was conducted. Cases were patients who were 18 years or older and who sustained a hip/femur fracture during the study period (1 January 1991–31 December 2002). Each case was matched to up to four control patients (PHARMO-RLS participants without any fracture during enrolment) by year of birth, gender, and region. The date of the first hip/femur fracture was defined as the index date. Each control was assigned the index date of the matched case.

Exposure assessment

In Dutch pharmacies, respiratory medications are usually dispensed for 3 months use. Therefore, current exposure was defined as the dispensing of at least one short acting beta-2 agonist (albuterol, fenoterol, terbutaline) or long acting beta-2 agonist (salmeterol, formoterol) in the 4 months before the index date. Past users were patients who received their last beta-2 agonist prescription more than 4 months before the index date. Cumulative exposure was calculated by summing the total amount of dispensed beta-2 agonists. The average daily dose was calculated by dividing the total cumulative dose by the total treatment time. We expressed dosages as albuterol equivalents using defined daily dosages.[14] We also measured indicators of severity of the underlying respiratory disease.[15] This included exposure to inhaled anticholinergics, inhaled and oral glucocorticoids, xanthine derivatives, acetylcystein and antibiotics within ± 3 days before or after an oral glucocorticoid prescription (a marker for an exacerbation[16]) 6 months prior to the index date. Moreover, hospitalisations for asthma/COPD in the 1-year before the index date and nebulised administration of respiratory medications in the 6 months before were also included as indicators of underlying disease severity. History of diseases and prior use of drugs that previously have been identified as general risk factors for fracture were treated as potential confounders.[17,18]

Conditional logistic regression was used to estimate odds ratios (OR) for fracture (SAS version 9.1.3, PHREG procedure). Two different adjustments were made in the regression analyses. The first analysis adjusted for indicators of the severity of the underlying disease. The second analysis adjusted not only for disease severity indicators but also for general risk factors. Backward selection of variables was used in the regression analyses. We also used smoothing spline regression plots (SAS version 9.1.3) to visualise the longitudinal relationship of risk of fracture with time between the index date and last dispensing of beta-2 agonists (recency of use).[19]

RESULTS

We identified 6763 patients who suffered hip/femur fracture. They were matched to 26 341 controls. The

DOI: 10.1002/pds

Table 1. Characteristics of cases and controls

	Cases ($n = 6763$)	Control subjects ($n = 26\,341$)	Univariate analysis
			OR (95% CI)
Average age (years)	75.7	75.3	
Number females (%)	4929 (73%)	19 138 (73%)	
Use 6 months before index date			
Short acting beta-2 agonists	388 (6%)	1100 (4%)	1.41 (1.25–1.59)
Long acting beta-2 agonists	148 (2%)	488 (2%)	1.21 (1.00–1.46)
Anticholinergics	323 (5%)	1002 (4%)	1.27 (1.12–1.45)
Xanthine derivatives	131 (2%)	281 (1%)	1.85 (1.56–2.29)
N-Acetylcystein	278 (4%)	803 (3%)	1.37 (1.19–1.57)
Inhaled glucocorticoids	437 (6%)	1316 (5%)	1.32 (1.18–1.42)
Oral glucocorticoids	366 (5%)	918 (3%)	1.59 (1.40–1.80)
Beta-blockers	957 (14%)	4068 (15%)	0.91 (0.84–0.98)
Hospitalisations ever before index date			
Cardiovascular disease	359 (5%)	1289 (5%)	1.10 (0.98–1.25)
Cerebrovascular disease	296 (4%)	565 (2%)	2.12 (1.84–2.45)
Rheumatoid arthritis	245 (4%)	731 (3%)	1.34 (1.16–1.56)

average age of cases was 75 years, and 73% were female (Table 1). The average time-period with prescribing data prior to the index date was 4.1 years (interquartile range 1.2–6.4 years). There were a total number of 41 740 prescriptions for bronchodilators: 26 204 (62.8%) for albuterol, 2123 (5.1%) for fenoterol, 3921 (9.4%) for terbutaline, 6598 (15.8%) for salmeterol and 2882 (6.9%) for formoterol. Among current beta-2 agonist users, the average daily dose was 967 μg albuterol equivalent for cases, and 829 μg albuterol equivalent for controls. 6.0% of current beta-2 agonist users had been prescribed oral glucocorticoids with a daily dose $\geq$7.5 mg prednisolone equivalent in the 6 months prior to the index date.

Indicators of the severity of the respiratory disease were associated with increased risk of hip/femur fracture. If patients had been hospitalised for asthma/COPD in the 1-year before, the crude OR for hip/femur fracture was 2.17 (95% confidence interval (CI), 1.41–3.34). Prior use of oral glucocorticoids in the 6 months before was also associated with an increased risk of hip/femur fracture. At an average daily dose of $<$7.5 mg prednisolone equivalents, the crude OR was 1.41 (95% CI, 1.17–1.69), at 7.5–15 mg daily this OR was 2.23 (95% CI, 1.74–2.86), and at $\geq$15 mg daily this OR was 2.64 (95% CI, 1.85–3.77).

General risk factors that were associated with increased hip/femur fracture risk included use of benzodiazepines 3 months prior to the index date (OR 1.44; 95% CI, 1.33–1.56), antipsychotics (OR 1.79; 95% CI, 1.58–2.02), antidepressants (OR 2.00; 95% CI, 1.81–2.21), anticonvulsants (OR 2.23; 95% CI, 1.90–2.61), anti-diabetic agents (OR 1.37; 95% CI, 1.25–1.49), disease modifying anti-rheumatic drugs (DMARDs) (OR 2.27; 95% CI, 1.80–2.86), and $\geq$2 prescriptions for a non-steroidal anti-inflammatory agent (NSAID, OR 1.46; 95% CI, 1.35–1.59). In addition, a history of anaemia (OR 2.41; 95% CI, 1.71–3.39), mental disorders (OR 2.54; 95% CI, 1.51–4.27), endocrine disorders (OR 2.10; 95% CI, 1.76–2.51), cerebrovascular disease (OR 2.12; 95% CI, 1.84–2.45) and inflammatory bowel disease (OR 1.72; 95% CI, 1.25–2.36) were also associated with increased risk of hip/femur fracture. In contrast, hip/femur fracture risk was reduced in subjects who were treated with beta-blockers (OR 0.91; 95% CI, 0.84–0.98) 6 months before the index date.

Current exposure to beta-2 agonists increased risk of hip/femur fracture in the univariate analysis (OR 1.39; 95% CI, 1.24–1.56) (Table 2). After adjustment for indicators of severity of the underlying disease, use of beta-2 agonists was no longer associated with risk of fracture (OR 1.15; 95% CI, 0.98–1.35). Further adjustment for general risk factors of fracture risk did not modify the risk of hip/femur fracture (OR 1.12; 95% CI, 0.95–1.31). The risk of hip/femur fracture increased with higher daily and cumulative dose of beta-2 agonists (Table 2). In patients using a daily dose of $>$1600 μg albuterol equivalents, the risk of hip/femur fracture was increased by 46% (OR 1.46; 95% CI, 1.02–2.08). There were no substantial differences between short-acting (OR 1.16; 95% CI, 0.98–1.38) and long-acting beta-2 agonists (OR 0.97; 95% CI, 0.74–1.27). Figure 1 shows the association between time since last beta-2 agonist prescription and risk of

DOI: 10.1002/pds

Table 2. Use of beta-2 agonists and risk of hip/femur fracture

Beta-2 agonists use	Cases ($n=6763$)	Controls ($n=26\,341$)	Univariate analysis	Multivariate analysis I[†]	Multivariate analysis II[‡]
			OR (95% CI)	OR (95% CI)	OR (95% CI)
Never use	5926 (87.6%)	23 690 (89.9%)	1.00	1.00	1.00
Past use	395 (5.8%)	1366 (5.2%)	1.16 (1.03–1.30)	1.10 (0.98–1.24)	1.03 (0.91–1.17)
Current use	442 (6.5%)	1285 (4.9%)	1.39 (1.24–1.56)	1.15 (0.98–1.35)	1.11 (0.95–1.31)
Cumulative dose					
<250 mg	133 (2.0%)	498 (1.9%)	1.08 (0.89–1.31)	1.06 (0.76–1.48)	1.00 (0.71–1.40)
250–1000 mg	145 (2.1%)	383 (1.5%)	1.52 (1.25–1.85)	1.50 (1.07–2.11)	1.42 (1.01–2.00)
> = 1000 mg	164 (2.4%)	404 (1.5%)	1.66 (1.37–2.00)	1.53 (1.06–2.20)	1.43 (0.99–2.07)
Average daily dose[*]					
≤400 μg	106 (1.6%)	359 (1.4%)	1.19 (0.95–1.48)	1.09 (0.86–1.38)	1.00 (0.79–1.28)
401–800 μg	113 (1.7%)	359 (1.4%)	1.28 (1.03–1.58)	1.08 (0.85–1.38)	1.05 (0.82–1.34)
801–1600 μg	131 (1.9%)	333 (1.3%)	1.60 (1.31–1.97)	1.27 (0.98–1.63)	1.26 (0.97–1.63)
>1600 μg	58 (0.9%)	121 (0.5%)	1.94 (1.41–2.66)	1.46 (1.02–2.08)	1.47 (1.02–2.10)
Not classified[§]	34 (0.5%)	113 (0.4%)	1.21 (0.82–1.78)	1.14 (0.77–1.69)	1.10 (0.74–1.64)

[*]Average daily dose: cumulative exposure divided by the treatment time.
[†]Adjusted for indicators of the severity of the underlying respiratory disease (i.e. use of inhaled glucocorticoids, anticholinergics, xanthines, acetylcystein, average daily dose of oral glucocorticoids, use of nebulised medication, ≥1 exacerbations, and ≥1 asthma/COPD hospitalisations).
[‡]Adjusted for indicators of the severity of the underlying respiratory disease (listed under †) and general risk factors of fracture risk (i.e. use of benzodiazepines, hormone replacement therapy, antipsychotics, antidepressants, beta-blockers, anticonvulsants, antidiabetics, two or more NSAID prescriptions, disease modifying anti-rheumatic drugs, anaemia, mental disorders, cerebrovascular disease, heart failure, endocrine disorders and inflammatory bowel disease).
[§]Not classified: average daily dose could not be determined for current beta-2 agonist users with only one prior prescription.

hip/femur fracture. The risk of fracture was increased particularly in patients who were recently exposed to beta-2 agonists.

After exclusion of patients who were exposed to oral glucocorticoids, the risk of hip/femur was no longer statistically significantly increased in any of daily or cumulative dose categories of beta-2 agonists (Table 3). In patients using a daily dose of >1600 μg albuterol equivalents without prior exposure to oral glucocorticoids, the OR of hip/femur was 1.31 (95%

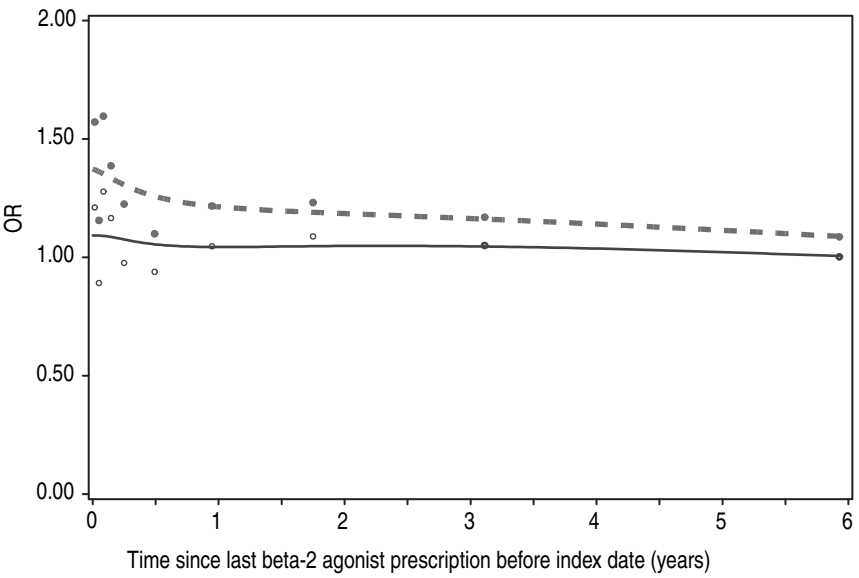

Figure 1. Recency of beta-2 agonist use before the index date and risk of hip/femur fracture. Key: dashed line: crude ORs; solid line: adjusted ORs. Adjustments were made for the same indicators of severity of OAD and general risk factors as in Table 2 (see footnote ‡)

DOI: 10.1002/pds

Table 3. Daily dose of beta-2 agonists and risk of hip/femur fracture in patients not exposed to oral glucocorticoids

Beta-2 agonists use	Cases ($n = 6274$)	Controls ($n = 23\,339$)	Univariate analysis	Multivariate analysis[†]
			OR (95% CI)	OR (95% CI)
Never use	5700	21 450	1.00	1.00
Past use	320	1104	1.08 (0.95–1.23)	0.99 (0.87–1.14)
Current use	254	785	1.21 (1.04–1.39)	1.00 (0.83–1.21)
Cumulative dose				
<250 mg	90	349	0.98 (0.77–1.24)	0.86 (0.67–1.11)
250–1000 mg	82	228	1.33 (1.03–1.72)	1.16 (0.87–1.54)
> = 1000 mg	82	207	1.45 (1.12–1.88)	1.15 (0.84–1.56)
Average daily dose[*]				
≤400 μg	65	245	0.99 (0.75–1.30)	0.84 (0.62–1.13)
401–800 μg	67	204	1.23 (0.93–1.63)	1.05 (0.77–1.42)
801–1600 μg	71	185	1.43 (1.08–1.89)	1.19 (0.86–1.64)
>1600 μg	26	61	1.56 (0.98–2.48)	1.31 (0.80–2.15)
Not classified[‡]	25	90	1.05 (0.67–1.64)	0.94 (0.59–1.48)

[*]Average daily dose: cumulative exposure divided by the treatment time.
[†]Adjusted for use of inhaled glucocorticoids, anticholinergics, xanthines, acetylcystein, nebulised medication, ≥1 asthma/COPD hospitalisations, use of benzodiazepines, hormone replacement therapy, antipsychotics, antidepressants, beta-blockers, anticonvulsants, antidiabetics, two or more NSAID prescriptions, disease modifying anti-rheumatic drugs, anaemia, mental disorders, cerebrovascular disease, heart failure, endocrine disorders and inflammatory bowel disease.
[‡]Not classified: average daily dose could not be determined for current beta-2 agonist users with only one prior prescription.

CI, 0.80–2.15). To further examine the role of the severity of the underlying disease, we also evaluated the association between risk of hip/femur fracture and other respiratory medication. It was found that the risk of hip/femur fracture increased with higher daily doses of all different respiratory medication (Figure 2). The risk of hip/femur fracture was statistically similar between users of higher doses of beta-2 agonists, inhaled glucocorticoids or inhaled anticholinergics.

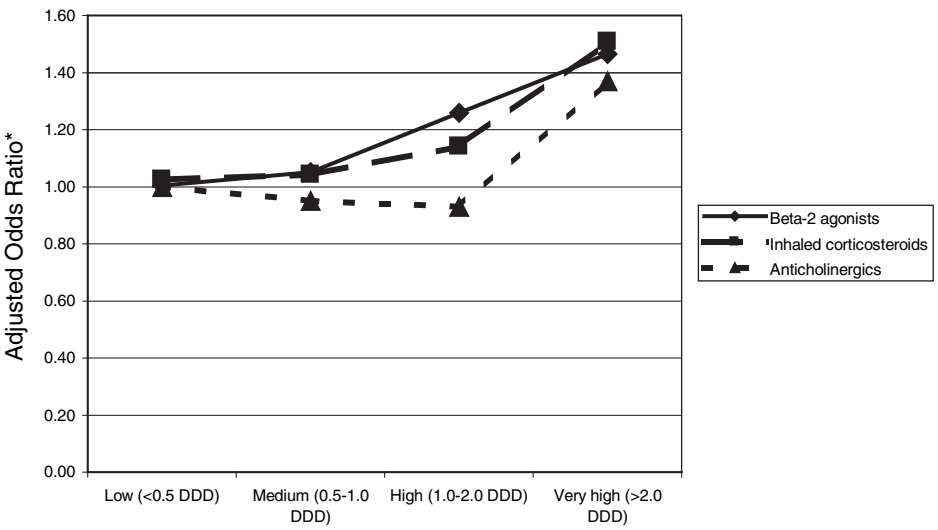

Figure 2. Risk of hip fracture among current users of beta-2 agonists, inhaled glucocorticoids or anticholinergics by average daily dose. Key: Y-axis: adjusted OR (adjusted for the same indicators of severity of OAD and general risk factors as in Table 2[*]). DDD: Defined daily dose. 1 DDD is equivalent to 800 μg inhaled albuterol, 800 μg inhaled beclomethasone diproprionate or 120 μg iptratropriumbromide

DOI: 10.1002/pds

DISCUSSION

In this study, we found increases in the risk of hip/femur fracture in patients using higher doses of beta-2 agonists. However, the excess risk of hip/femur fracture substantially reduced after exclusion of oral glucocorticoid users and after adjustment for indicators of underlying disease severity. Also, the risk of hip/femur fracture was similar between users of beta-2 agonists, inhaled glucocorticoids and anticholinergics.

The autonomic nervous system is involved in regulation of bone remodelling. Leptin, a hormone that is produced in fat cells in order to signal food intake and body weight, regulates bone formation through the hypothalamus in mice.[1,20] Downstream the sympathetic signalling, stimulation of beta-2 receptors present on osteoblasts progenitor cells, results in an increased bone resorption by expression of the osteoclast differentiation factor RANKL.[2] Systemic administration of beta-2 agonists like albuterol and clenbuterol had a negative effect on bone mineral density and microarchitecture of trabecular bone in rats.[3] Systemic administration of clenbuterol inhibited femoral bone growth, and decreased bone mineral content and bone mineral density.[21] Isoprotenerol, another beta-2 agonist, has shown to suppress bone formation in mice. The same study revealed a specific role of the sympathetic nervous system in unloading-induced bone loss.[22] Conversely, bone mineral density, bone mass and femoral torsional strength in rats were increased after systemic administration of the beta-blocker propranolol.[1,4]

Observational studies in humans have shown conflicting results on the association between use of beta-blockers and reduced risk of fracture or increased in bone mineral density.[5–7,23–25] Preliminary results from a randomised controlled clinical trial did not show a fracture risk reduction among users of the non-cardioselective beta-blocker carvedilol.[26] Another randomised controlled trial found that intake of the non-cardioselective beta-blocker propranolol did not change markers of bone formation.[7] The reason for this lack of consistent effects of beta-blockers in humans is unknown. Although beta-blockers may have positive effects on the bone at very high doses in animals, this cannot generalise to humans with considerable lower doses. The concentration of beta-blockers in bone tissue is not known. For beta-2 agonists that are administered through inhalation, these levels are likely to be even lower. Average blood plasma concentration of albuterol after inhalation of 180 μg was found to be 1.5 ng/L compared to levels of carvedilol ranging from 21 to 161 μg/L after single 25--50 mg doses.[8,27–29] As blood plasma concentrations of oral carvedilol are at least 10 000 times higher than inhaled albuterol, it seems unlikely that albuterol intake would affect bone mineral metabolism.

This study found that patients using different respiratory medications had increased risks of fracture, especially at higher daily dose. The explanation for this increase could be adverse effects of the three different classes of respiratory medication or effects of the underlying respiratory disease. Increases in the risk of fracture have been reported for inhaled glucocorticoids, but there is controversy about the explanation of this increased risk.[15,30] There is no evidence for a causal relationship between intake of inhaled anticholinergics and risk of hip/femur fracture. Obstructive airway disease itself has been associated with decreased bone mineral density, independent of oral glucocorticoid exposure.[31,32] The underlying mechanisms for this may include lack of physical activity,[33,34] low body mass index among patients with COPD,[35] smoking,[36] decreased testosterone levels,[37] hypercapnia[38] and chronic inflammation. Cytokines that are expressed in inflammatory diseases, such as asthma and/or COPD, include tumour necrosis factor (TNF)-a, transforming growth factor-b, interleukin (IL)-1b, IL-4 and IL-8. These cytokines have been shown to affect bone remodelling *in vivo* and *in vitro*.[39–45] In this study, adjustment for several proxy indicators of disease severity substantially reduced the excess risk of fracture in patients using beta-2 agonists. Given the inverse association between lung function and bone mineral density,[31] it appears likely that further adjustment with lung function would further decrease this small excess risk.

This study has several limitations. The PHARMO-RLS database lacks detailed information on the severity of respiratory disease such as lung function measurements. But even with proxy indicators of disease severity, we found that the risk of hip/femur fracture reduced substantially after adjustment. Moreover, data on smoking,[36] body mass index or fat free mass[46] and data on exercise were not available. Therefore, we cannot exclude the possibility that unmeasured confounding has biased our findings. But it is likely that adjustment for these factors would have further reduced the excess risk of hip/femur fracture in patients using beta-2 agonists. Also, we did not have information on the timing of drug intake by patients, only on the timing of drug dispensing. With more than

DOI: 10.1002/pds

6700 hip/femur fractures, our study had a reasonable sample size to study our hypothesis. We were able to match almost each case patients to up to 4 controls by age, gender and region in order to minimise confounding by matching variables. Our findings of an increased risk of hip fracture with the use of oral glucocorticoids,[47] benzodiazepines,[48,49] antidepressants[48] and anticonvulsants[50] are similar to those of previous studies.

In conclusion, we found that patients who suffer from severe obstructive airway disease are at increased risk of hip/femur fracture. A dose-response association was apparent not only among users of beta-2 agonists, but also among users of other types of respiratory medications. This suggests that the severity of the underlying disease, rather than the use of beta-2 agonists, may play an important role in the aetiology of hip/femur fractures in patients using beta-2 agonists.

REFERENCES

1. Takeda S, Elefteriou F, Levasseur R, *et al*. Leptin regulates bone formation via the sympathetic nervous system. *Cell* 2002; **111**(3): 305–317.
2. Elefteriou F, Ahn JD, Takeda S, *et al*. Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature* 2005; **434**(7032): 514–520.
3. Bonnet N, Benhamou CL, Brunet-Imbault B, *et al*. Severe bone alterations under beta2 agonist treatments: Bone mass, microarchitecture and strength analyses in female rats. *Bone* 2005; **37**(5): 622–633.
4. Minkowitz B, Boskey AL, Lane JM, *et al*. Effects of propranolol on bone metabolism in the rat. *J Orthop Res* 1991; **9**(6): 869–875.
5. Pasco JA, Henry MJ, Sanders KM, *et al*. Beta-adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J Bone Miner Res* 2004; **19**(1): 19–24.
6. Schlienger RG, Kraenzlin ME, Jick SS, *et al*. Use of beta-blockers and risk of fractures. *Jama* 2004; **292**(11): 1326–1332.
7. Reid IR, Lucas J, Wattie D, *et al*. Effects of a beta-blocker on bone turnover in normal postmenopausal women: a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90**(9): 5212–5216.
8. Anderson PJ, Zhou X, Breen P, *et al*. Pharmacokinetics of (R,S)-Albuterol after aerosol inhalation in healthy adult volunteers. *J Pharm Sci* 1998; **87**(7): 841–844.
9. Lipworth BJ. Risks versus benefits of inhaled beta 2-agonists in the management of asthma. *Drug Saf* 1992; **7**(1): 54–70.
10. Kiely DG, Cargill RI, Grove A, *et al*. Abnormal myocardial repolarisation in response to hypoxaemia and fenoterol. *Thorax* 1995; **50**(10): 1062–1066.
11. van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. *J Bone Miner Res* 2001; **16**(3): 581–588.
12. Herings RM. PHARMO: a record linkage system for postmarketing surveillance of prescription drugs in The Netherlands: Utrecht University, 1993.
13. Herings RM, Stricker BH, de Boer A *et al.* Current use of thiazide diuretics and prevention of femur fractures. *J Clin Epidemiol*. 1996; **49**(1): 115–119.
14. Anonymous ATC classification index with DDDs2002. Nydalen: WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health, 2002.
15. de Vries F, van Staa TP, Bracke MS, *et al*. Severity of obstructive airway disease and risk of osteoporotic fracture. *Eur Respir J* 2005; **25**(5): 879–884.
16. Van Ganse E, van der Linden PD, Leufkens HG, *et al*. Asthma medications and disease exacerbations: an epidemiological study as a method for asthma surveillance. *Eur Respir J* 1995; **8**(11): 1856–1860.
17. Cummings SR, Nevitt MC, Browner WS, *et al*. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; **332**(12): 767–773.
18. Grisso J, Capezuti E, Schwartz A. *Falls as risk factors for fractures*. In Marcus R, Feldman D, Kelsey J (eds). *Osteoporosis. San Diego*. Academic Press: California; 1996, 599–611.
19. Greenland S, Dose-response and, trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology* 1995; **6**(4): 356–365.
20. Ducy P, Amling M, Takeda S, *et al*. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell* 2000; **100**(2): 197–207.
21. Kitaura T, Tsunekawa N, Kraemer WJ. Inhibited longitudinal growth of bones in young male rats by clenbuterol. *Med Sci Sports Exerc* 2002; **34**(2): 267–273.
22. Kondo H, Nifuji A, Takeda S, *et al*. Unloading induces osteoblastic cell suppression and osteoclastic cell activation to lead to bone loss via sympathetic nervous system. *J Biol Chem* 2005; **280**(34): 30192–30200.
23. Levasseur R, Dargent-Molina P, Sabatier JP, *et al*. Beta-blocker use, bone mineral density, and fracture risk in older women: results from the Epidemiologie de l'Osteoporose prospective study. *J Am Geriatr Soc* 2005; **53**(3): 550–552.
24. Lynn H, Kwok T, Wong SY, *et al*. Angiotensin converting enzyme inhibitor use is associated with higher bone mineral density in elderly Chinese. Bone 2005.
25. Rejnmark L, Vestergaard P, Kassem M, *et al*. Fracture risk in perimenopausal women treated with beta-blockers. *Calcif Tissue Int* 2004; **75**(5): 365–372.
26. Reid IR, Gamble GD, Grey AB, *et al*. beta-Blocker use, BMD, and fractures in the study of osteoporotic fractures. *J Bone Miner Res* 2005; **20**(4): 613–618.
27. McPhillips JJ, Schwemer GT, Scott DI, *et al*. Effects of carvedilol on blood pressure in patients with mild to moderate hypertension. A dose response study. *Drugs* 1988; **36**(Suppl 6): 82–91.
28. Neugebauer G, Akpan W, von Mollendorff E, *et al*. Pharmacokinetics and disposition of carvedilol in humans. *J Cardiovasc Pharmacol* 1987; **10**(Suppl 11): S85–S88.
29. Louis WJ, McNeil JJ, Workman BS, *et al*. A pharmacokinetic study of carvedilol (BM 14.190) in elderly subjects: preliminary report. *J Cardiovasc Pharmacol* 1987; **10**(Suppl 11): S89–S93.
30. Hubbard RB, Smith CJ, Smeeth L, *et al*. Inhaled corticosteroids and hip fracture: a population-based case-control study. *Am J Respir Crit Care Med* 2002; **166**(12 Pt 1): 1563–1566.
31. Sin DD, Man JP, Man SF. The risk of osteoporosis in Caucasian men and women with obstructive airways disease. *Am J Med* 2003; **114**(1): 10–14.
32. Lekamwasam S, Trivedi DP, Khaw KT. An association between respiratory function and bone mineral density in women from the general community: a cross sectional study. *Osteoporos Int* 2002; **13** (9): 710–715.

33. Ford ES, Heath GW, Mannino DM, *et al*. Leisure-time physical activity patterns among US adults with asthma. *Chest* 2003; **124**(2): 432–437.
34. Malkia E, Impivaara O. Intensity of physical activity and respiratory function in subjects with and without bronchial asthma. *Scand J Med Sci Sports* 1998; **8**(1): 27–32.
35. Incalzi RA, Caradonna P, Ranieri P, *et al*. Correlates of osteoporosis in chronic obstructive pulmonary disease. *Respir Med* 2000; **94**(11): 1079–1084.
36. Kanis JA, Johnell O, Oden A, *et al*. Smoking and fracture risk: a meta-analysis. *Osteoporos Int* 2005; **16**(2): 155–162.
37. Kamischke A, Kemper DE, Castel MA, *et al*. Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. *Eur Respir J* 1998; **11**(1): 41–45.
38. Dimai HP, Domej W, Leb G, *et al*. Bone loss in patients with untreated chronic obstructive pulmonary disease is mediated by an increase in bone resorption associated with hypercapnia. *J Bone Miner Res* 2001; **16**(11): 2132–2141.
39. Lam J, Takeshita S, Barker JE, *et al*. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest* 2000; **106**(12): 1481–1488.
40. Jilka RL, Weinstein RS, Bellido T, *et al*. Osteoblast programmed cell death (apoptosis): modulation by growth factors and cytokines. *J Bone Miner Res* 1998; **13**(5): 793–802.
41. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature* 2003; **423**(6937): 337–342.
42. Hock JM, Krishnan V, Onyia JE, *et al*. Osteoblast apoptosis and bone turnover. *J Bone Miner Res* 2001; **16**(6): 975–984.
43. Chung K. Cytokines. In *Asthma and COPD. Basic mechanisms and clinical management*. Barnes P, Drazen J, Rennard S, Thompson N (eds). Academic Press: London, 2002.
44. Okada Y, Morimoto I, Ura K, *et al*. Short-term treatment of recombinant murine interleukin-4 rapidly inhibits bone formation in normal and ovariectomized mice. *Bone* 1998; **22**(4): 361–365.
45. Bendre MS, Montague DC, Peery T, *et al*. Interleukin-8 stimulation of osteoclastogenesis and bone resorption is a mechanism for the increased osteolysis of metastatic bone disease. *Bone* 2003; **33**(1): 28–37.
46. Bolton CE, Ionescu AA, Shiels KM, *et al*. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **170**(12): 1286–1293.
47. Van Staa TP, Leufkens HG, Abenhaim L, *et al*. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000; **15**(6): 993–1000.
48. Liu B, Anderson G, Mittmann N, *et al*. Use of selective serotonin-reuptake inhibitors of tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet* 1998; **351**(9112): 1303–1307.
49. Herings RM, Stricker BH, de Boer A, *et al*. Benzodiazepines and the risk of falling leading to femur fractures. Dosage more important than elimination half-life. *Arch Intern Med* 1995; **155**(16): 1801–1807.
50. Souverein PC, Webb DJ, Petri H, *et al*. Incidence of fractures among epilepsy patients: a population-based retrospective cohort study in the General Practice Research Database. *Epilepsia* 2005; **46**(2): 304–310.

DOI: 10.1002/pds