

ORIGINAL REPORT

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

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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 ≥ 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

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[†]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 exacerbation¹⁶) 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

Table 1. Characteristics of cases and controls

	Cases (<i>n</i> = 6763)	Control subjects (<i>n</i> = 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 ≥ 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 ≥ 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 ≥ 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

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%

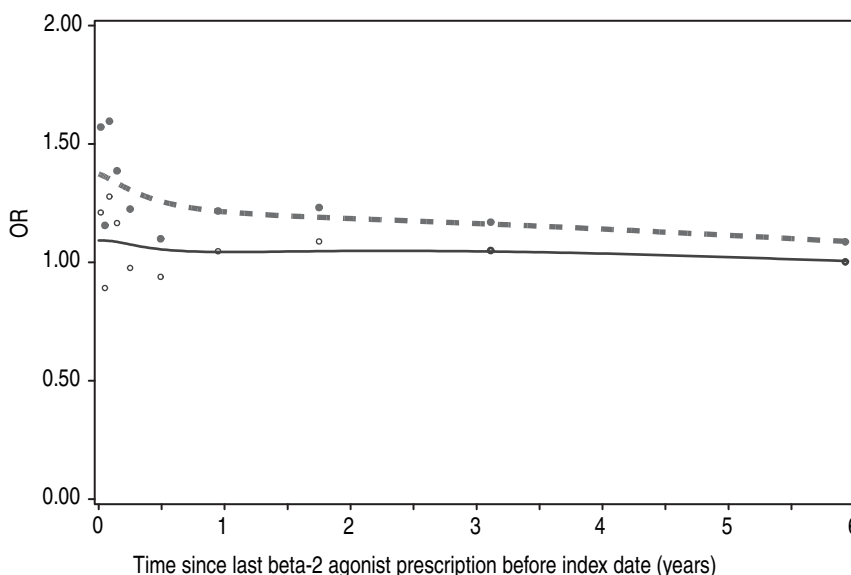


Figure 1. Recency of beta-2 agonist use before the index date and risk of hip/femur fracture. Key: dashed line: crude ORs; solid line: adjusted ORs. Adjustments were made for the same indicators of severity of OAD and general risk factors as in Table 2 (see footnote [‡])

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, anti-diabetics, 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.

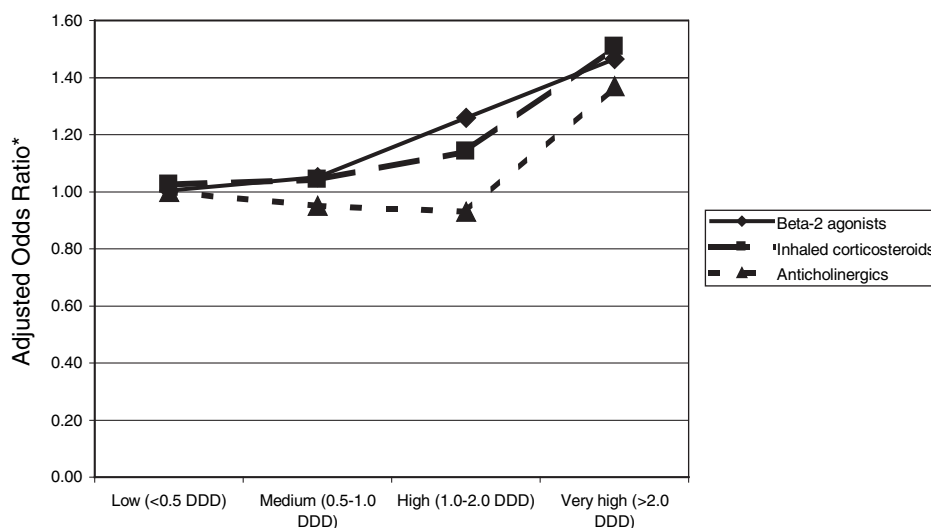


Figure 2. Risk of hip fracture among current users of beta-2 agonists, inhaled glucocorticoids or anticholinergics by average daily dose. Key: Y-axis: adjusted OR (adjusted for the same indicators of severity of OAD and general risk factors as in Table 2*). DDD: Defined daily dose. 1 DDD is equivalent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

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 Isoproterenol, 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 hypercapnia³⁸ and chronic inflammation. Cytokines that are expressed in inflammatory diseases, such as asthma and/or COPD, include tumour necrosis factor (TNF)-α, transforming growth factor-β, interleukin (IL)-1β, 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 mass⁴⁶ 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

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} antidepressants⁴⁸ and anticonvulsants⁵⁰ 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.

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