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CHEST

Original Research

DRUG-INDUCED FRACTURE RISK

Fracture Risk in Patients With Chronic Lung Diseases Treated With Bronchodilator Drugs and Inhaled and Oral Corticosteroids*

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Background: **Chronic lung diseases and drugs used to treat patients with chronic lung diseases may be associated with an increased fracture risk.**
Methods: **The design was a case-control study of all patients with a fracture (n = 124,655) in the year 2000 in Denmark as case subjects. For each case subject, three age- and gender-matched control subjects were randomly drawn from the general population (n = 373,962).**
Results: **Chronic lung diseases such as COPD (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.13 to 1.25), emphysema (OR, 1.31; 95% CI, 1.16 to 1.48), and other chronic lung diseases (OR, 1.20; 95% CI, 1.00 to 1.44) were associated with a higher relative risk of any fracture than asthma (OR, 1.06; 95% CI, 1.01 to 1.12). Oral corticosteroids were associated with a dose-dependent increased risk of fractures. Inhaled short-acting β-agonists were associated with an increase in fracture risk that was not dose dependent and was seen already at low doses. Oral β-agonists were associated with an increase in fracture risk at low doses but not at higher doses. Other bronchodilators (inhaled long-acting β-agonists, inhaled β-agonists plus inhaled corticosteroids, inhaled β-agonists plus antimuscarinic substances, inhaled antimuscarinic substances, inhaled cromoglycate and cromoglycate-like substances, oral theophylline, and oral leukotriene receptor antagonists), and inhaled corticosteroids were not associated with fracture risk.**
Conclusions: **The increase in fracture risk seen with inhaled short-acting β-agonists may be linked to the severity of the underlying lung disease rather than with the β-agonists, *per se*, as other types of β-agonists were not associated with fractures.** ***(CHEST 2007; 132:1599–1607)***

Key words: asthma; β-agonist; COPD; corticosteroid; cromoglycate; emphysema; fracture; leukotriene receptor antagonists; theophylline

Abbreviations: BMD = bone mineral density; CI = confidence interval; DDD = defined daily dose; GP = general practitioner; LABA = long-acting β-agonist; OR = odds ratio

Lung diseases may be associated with osteoporosis and thus fractures[1] through a number of mechanisms. The patients are often immobilized due to their reduced lung function, which may lead to disuse osteoporosis, and retention of carbon dioxide with disturbances in acid balance leads to a decrease in bone mineral density (BMD).[2] Patients with advanced pulmonary disease may also be malnourished and underweight with deficiency in, *eg*, vitamin D, which may also be linked to decreased BMD.[3] Some lung diseases may also be accompanied by an increased production of cytokines, which may increase bone resorption.[4] Finally, many lung diseases require treatment with oral corticosteroids, which may lead to a decreased BMD[5] and an increased risk of fractures.[6] Prior studies have indicated that use of inhaled corticosteroids may be associated with a small decrease in BMD[7] and a limited increase in fracture risk at high doses,[8] but have also indicated that the increase may not be due to the inhaled corticosteroids *per se* but rather to the severity of the lung disease for which they were prescribed.[9] This phenomenon is known as confounding by indication: more severe cases of a disease being more likely to receive a particular drug in high doses for a prolonged period of time, the effect of the disease thus

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being confounded with the effect of the drugs. Inhaled bronchodilators have been associated with an increased fracture risk,[10] perhaps from the same mechanisms as inhaled corticosteroids. However, it is unknown if large doses are associated with an increased fracture risk, and whether differences exist between short-acting and long-acting inhaled β-agonists (LABAs). Osteoblasts possess β_2-adrenergic receptors,[11] and β-receptor blockers have been associated with a decreased risk of fractures.[12] β-Receptor agonists may thus theoretically increase fracture risk besides the effects of the underlying lung disease. Little is known about the effects of other bronchodilators and lung active drugs on bone metabolism, bone density, and fracture risk. No clinical studies exist for leukotriene receptor antagonists or inhaled antimuscarinic drugs, although data from a cell model indicated that leukotriene B_4 stimulates osteocalcin but not alkaline phosphatase in normal osteoblasts.[13] However, this is probably not relevant because montelukast antagonizes the effects of the cysteinyl leukotrienes but not leukotriene B_4. For theophylline, one *in vitro* study[14] is available, but the clinical implications of the findings are not known. For cromoglycate, three studies[15–17] are available reporting no change in BMD; however, no fracture data are available. Fracture studies are therefore needed. As these drugs are in widespread use, even small changes in fracture risk associated with their use may have significant impact on the number of fractures on a population level. The aim of the study was thus to assess if the use of any bronchodilator or other lung active drug for asthma, COPD, emphysema, or other lung disease was associated with a change in the risk of fractures.

Materials and Methods

In Denmark, the extensive nature of registers covering contacts to the health sector offers good possibilities for studies on the occurrence of fractures.[18] Using the unique 10-digit civil registry number that is assigned to all Danish citizens shortly after birth, a complete hospital discharge and prescription history can be established for each individual, and valid linkage between population-based registries can be obtained. The unique civil registry number is used in all registers: if a person buys a drug on prescription, the drug is registered as bought by this individual, and the same calls for admissions to hospitals and contacts to general practitioners (GPs) for reimbursement purposes. The study was subject to control by the National Board of Health, and the Danish Data Protection Agency.

Study Design

The study was designed as a case-control study. Case subjects were those subjects who sustained a fracture during the year 2000. Control subjects were matched subjects without a fracture in the year 2000. Exposure was use of drugs and diseases before the date of fracture or a matched dummy date in the control subjects.

Identification of Fracture Cases

In Denmark, The National Hospital Discharge Register covers all contacts (on inpatient basis or outpatient basis) to the hospitals.[19] The register was founded in 1977, but outpatient records were first completely incorporated from 1995. The files of The National Hospital Discharge Register include information on the civil registry number of the patient, date of discharge, and discharge diagnoses assigned exclusively by the physician at discharge according to the Danish version of the International Classification of Diseases, Eighth Revision until the end of 1993, and to the Danish version of the International Classification of Diseases, Tenth Revision. The register has nationwide coverage of public hospitals with an almost 100% completeness of recordings and a high precision of diagnoses,[19] especially of fracture diagnoses.[20] Using The National Hospital Discharge Register, we identified all subjects who had sustained a fracture between January 1, 2000, and December 31, 2000 (n = 124,655).

Selection of Population-Based Control Subjects

Using the Civil Registration System, which has electronic records on all changes in vital status, including change of address and date of death for the entire Danish population since 1968, we randomly selected three control subjects for each case subjects, matched by year of birth. This matching on age and gender was performed in order to ensure age and gender adjustment. The control subjects were selected using the incidence-density sampling technique[21]: control subjects had to be alive and at risk for fracture diagnosis at the time the corresponding case was diagnosed. A total of 373,962 control subjects were included in the study.

Data on Use of Oral and Inhaled Bronchodilators and Corticosteroids

In Denmark, pharmacies have computerized systems for recording prescriptions. The prescription database includes information on the patient's civil registry number, the type and amount of drug prescribed according to the Anatomical Therapeutical Chemical classification system,[22,23] and the date the prescription was filled.

The dose of the drug bought during the observation period was expressed as defined daily doses (DDDs). One DDD is the dose that a person on average uses of the drug in 1 day. Standard conversion formulas exist for the various drugs. DDD was chosen as exposure variable to allow comparison of drug classes. The DDD system used is validated and based on the World Health Organization Collaborating Centre for Drug Statistics Methodology.[24]

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Within the prescription database, we identified all prescriptions for inhaled β-agonists (classified as short-acting β-agonists and LABAs), inhaled β-agonists combined with antimuscarinic substances (*eg*, ipratropium), inhaled β-agonists combined with inhaled corticosteroids (budesonide, fluticasone), inhaled corticosteroids, inhaled antimuscarinic substances, oral β-agonists, oral theophylline or theophylline-like substances, inhaled cromoglycate or cromoglycate like substances, and oral leukotriene receptor antagonists from January 1, 1996, to the date of fracture or censoring among case subjects and control subjects. The exposure was calculated as the sum of redeemed DDDs and as the average daily dose (number of defined daily dosages DDD per day).

Data on Confounding Factors

We adjusted for underlying lung disease using the following categories: (1) asthma, (2) COPD, (3) emphysema, and (4) other chronic lung diseases (fibrosis, pneumoconiosis). The diagnosis of a disease was at the discretion of the physician treating the patient and was based on clinical findings including measurements of lung function. Using the National Hospital Discharge Register, number of days spent in hospital the year preceding fracture (year 1999), and a history of a prior fracture in the period from 1977 to 2000 were also included as confounders. Furthermore, our confounder analysis included data from the National Bureau of Statistics on income in 1999, social status in 1999, working status in 1999, educational status in 1999, and data from The National Health Organisation Register on number of contacts to GPs and practicing specialists for the period 1996 to 2000.

Information on alcoholism was collected as appearance of a diagnosis of alcoholism in the National Hospital Discharge Register[19] or in the Psychiatric Central Register,[25] or a prescription of disulfiram in the prescription database. Information on prior fractures was based on data from the National Hospital Discharge Register.[19]

Statistical Analysis

Data from the different registers were merged at the National Bureau of Statistics, and for each subject the 10-digit civil registry number was substituted by a unique case number; as investigators, we had no access to personally identifiable information. A conditional logistic regression analysis was performed. Analyses were performed using statistical software (STATA 8.1; Stata Corporation; College Station, TX; and SPSS 14.0; SPSS; Chicago IL, both in the Unix version).

Results

Table 1 shows baseline characteristics of the participants. The prevalence of lung diseases in general was higher among fracture case subjects than among control subjects, and the same was the case for use of most agents for lung diseases except for cromoglycate. A total of 26 patients had undergone lung transplantation with a significant excess risk among fracture case subjects (odds ratio [OR], 5.67; 95% confidence interval [CI], 2.53 to 12.7) [Table 1].

Table 2 shows the effects of presence of a chronic lung disease or use of drugs to treat lung diseases. COPD, emphysema, and other chronic lung diseases were associated with a higher OR of fracture than asthma. Oral corticosteroid use and use of inhaled β-agonists were associated with an increased risk of any fracture.

Table 3 shows that oral corticosteroids were associated with a dose-dependent increase in relative risk of any fracture. There was an increase in the risk of any fracture associated with inhaled short-acting β agonists that was not dose dependent, *ie*, the increase was present already at very low doses.

Table 4 shows the risk of any fracture associated with severity of the underlying lung disease. There was an increased risk of all lung diseases except the group of other lung diseases. There was a trend toward an increase in overall fracture risk with number of days spent in hospital for COPD (p for trend < 0.01), emphysema ($p = 0.02$), and asthma ($p < 0.01$), but not for other types of lung diseases ($p = 0.39$). Increasing number of contacts to a GP and specialist was also associated with an increase in relative risk of any fracture.

Table 5 shows the effect of drugs used to treat lung diseases on the risk of osteoporotic fractures (hip, forearm, and spine). Oral corticosteroids were associated with an increased fracture risk in a dose-dependent manner at all skeletal sites shown. However, the association differed between sites being stronger for spine than hip and forearm fractures. None of the other drugs were systematically associated with fracture risk. At high doses, there was a small increase in fracture risk for inhaled short-acting β agonists in the hip and spine but not in the forearm. There was no dose-response relationship for the spine fractures and inhaled short-acting β agonists, and only a borderline significant trend for the hip fractures ($p = 0.056$). Inhaled corticosteroids were associated with a decreased fracture risk in the hip, and the same occurred with low doses of inhaled LABAs.

Table 6 shows the effects of the underlying lung disease on osteoporotic fractures. Emphysema and the group of other lung disease were not associated with fracture risk. COPD was associated with an increased risk of hip fractures in a dose-dependent fashion: the risk of fractures increased with the duration of hospital stay and the number of contacts with doctors. COPD was in general not associated with forearm fractures, while a dose-dependent association was seen for spine fractures with a significant increase in the group with the most bed days in hospital. Asthma was not associated with spine fractures, while a non–dose-dependent association was seen with hip fractures, and a trend toward a dose-dependent association was seen for forearm frac-

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Table 1—*Characteristics of Case Subjects and Controls Subjects, Any Fracture

Variables	Case Subjects (n = 124,655)	Control Subjects (n = 373,962)	p Value
Age, yr	43.44 ± 27.39	43.44 ± 27.39	
Gender			
Male	60,107 (48.2)	180,321 (48.2)	
Female	64,548 (51.8)	193,641 (51.8)	
Annual income, US$	25,974 ± 22,385	27,955 ± 31,243	< 0.01
Living with someone	35,922 (29.0)	123,925 (33.4)	< 0.01
Living alone	88,150 (71.0)	247,196 (66.6)	
Working	41,380 (40.4)	137,751 (44.9)	< 0.01
Not working	60,953 (59.6)	168,725 (55.1)	
Previous fracture	41,315 (33.1)	56,200 (15.0)	< 0.01
Bed days in hospital in 1999	9.7 ± 39.7	4.2 ± 20.3	< 0.01
Contacts with GP or specialists in 1999	23.9 ± 43.3	18.1 ± 31.4	< 0.01
Use of antiosteoporotic drugs			
Any antiresorptive drug	12,900 (10.3)	28,101 (7.5)	< 0.01
Bisphosphonates	5,679 (4.6)	3,887 (1.0)	< 0.01
Hormone therapy†	440 (6.3)	244 (6.6)	< 0.01
Selective estrogen receptor modulators	7,789 (0.4)	24,623 (0.1)	< 0.01
Asthma	4,142 (3.3)	8,782 (2.3)	< 0.01
COPD	4,171 (3.3)	6,739 (1.8)	< 0.01
Emphysema	537 (0.4)	726 (0.2)	< 0.01
Other chronic lung diseases	213 (0.2)	356 (0.1)	< 0.01
Lung transplantation	17 (< 0.1)	9 (< 0.1)	< 0.01
Systemic oral corticosteroids	8,674 (7.0)	18,020 (4.8)	< 0.01
Inhaled corticosteroids	11,463 (9.2)	27,941 (7.5)	< 0.01
Inhaled short-acting β-agonists	15,304 (12.3)	36,594 (9.8)	< 0.01
Inhaled LABAs	3,311 (2.7)	7,045 (1.9)	< 0.01
Inhaled β-agonists plus corticosteroids	284 (0.2)	676 (0.2)	< 0.01
Inhaled β-agonists plus antimuscarinic substances	2,712 (2.2)	4,999 (1.3)	< 0.01
Oral β-agonists	11,391 (9.1)	30,372 (8.1)	< 0.01
Inhaled antimuscarinic substances	956 (0.8)	1,704 (0.5)	< 0.01
Inhaled cromoglycate	129 (0.1)	377 (0.1)	0.80
Peroral leukotriene receptor antagonists	832 (0.7)	1,604 (0.4)	< 0.01
Peroral theophylline	1,971 (1.6)	3,895 (1.0)	< 0.01

*Data are presented as mean ± SD or No. (%).
†Estrogen compounds with or without progestogens, women only.

tures. Changing the analyses in Tables 2–5 from cumulative to average daily dose did not change the results (data not shown).

Changing the analyses from number of bed days within the last year to duration of disease revealed a distinctive pattern with a decreasing risk of any fracture with increasing disease duration. For disease duration ≤ 3 years, 3.1 to 6 years, and > 6 years, the risk of any fracture compared to patients without any of the diseases in question, the OR declined from 1.24 (95% CI, 1.12 to 1.37), to > 1.15 (95% CI, 1.04 to 1.28), to 1.08 (95% CI, 1.00 to 1.15) for asthma, respectively. For COPD, the OR declined from 1.39 (95% CI, 1.30 to 1.49), to > 1.28 (95% CI, 1.17 to 1.40), to 1.16 (95% CI, 1.07 to 1.26). For emphysema, the OR declined from 1.56 (95% CI, 1.26 to 1.93), to > 1.43 (95% CI, 1.12 to 1.82), to 1.19 (95% CI, 0.99 to 1.43). For other chronic lung diseases, no apparent change with time was present (OR, 1.74 [95% CI, 1.12 to 2.70], to OR, 0.99 [95% CI, 0.61 to 1.62], to OR, 1.27 [95% CI, 1.02 to 1.59]). The other results were unchanged compared to Tables 3, 4. Age-stratified analyses (< 40 years, 40 to 79 years, and ≥ 80 years) did not systematically change the results (data not shown).

Discussion

In this large-scale, population-based, case-control study, we found no general association between drugs for lung diseases and fracture risk except for an increase in fracture risk with oral corticosteroids and inhaled short-acting β-agonists. For oral corticosteroids, a dose relationship with fracture risk was present, whereas no such relationship was seen for inhaled short-acting β-agonists. The only nonsignificant trend was seen for hip fractures with inhaled short-acting β-agonists (Table 5).

Inhaled short-acting β-agonists are most often used to control acute dyspnea, whereas the other

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Table 2—*Risk of Any Fracture Presented as Crude Risk or Adjusted Risk*

Variables	Crude OR (95% CI)	Adjusted for Other Variables Excluding Drug Use*, OR (95% CI)	Mutually Adjusted†, OR 95% CI)	Multiply Adjusted‡, OR (95% CI)
Asthma	1.43 (1.38–1.48)	1.14 (1.09–1.20)	1.13 (1.09–1.18)	1.06 (1.01–1.12)
COPD	1.89 (1.81–1.96)	1.31 (1.25–1.37)	1.45 (1.38–1.52)	1.19 (1.13–1.25)
Emphysema	2.22 (1.99–2.49)	1.36 (1.20–1.53)	1.34 (1.19–1.51)	1.31 (1.16–1.49)
Other chronic lung disease	1.80 (1.52–2.13)	1.21 (1.01–1.46)	1.27 (1.06–1.51)	1.20 (1.00–1.44)
Oral corticosteroids	1.48 (1.44–1.52)		1.29 (1.25–1.33)	1.14 (1.10–1.17)
Inhaled corticosteroids	1.25 (1.23–1.28)		0.95 (0.91–0.98)	0.96 (0.92–1.00)
Inhaled short-acting β-agonist	1.29 (1.27–1.32)		1.17 (1.14–1.20)	1.13 (1.10–1.17)
Inhaled LABA	1.42 (1.36–1.48)		0.99 (0.95–1.04)	0.99 (0.95–1.05)
β-Agonist and corticosteroid inhaled combined	1.26 (1.10–1.35)		0.88 (0.77–1.02)	0.88 (0.75–1.02)
β-Agonist and antimuscarinic substance inhaled combined	1.64 (1.57–1.72)		1.09 (1.03–1.16)	1.05 (0.99–1.12)
Oral β-agonist	1.14 (1.11–1.16)		1.05 (1.02–1.07)	1.02 (0.99–1.06)
Antimuscarinic substances inhaled	1.69 (1.56–1.83)		1.07 (0.99–1.17)	1.05 (0.96–1.14)
Cromoglycate	1.03 (0.84–1.25)		0.86 (0.71–1.06)	0.80 (0.65–1.00)
Leukotriene receptor antagonists	1.56 (1.43–1.70)		0.97 (0.89–1.06)	1.03 (0.94–1.14)
Theophylline	1.53 (1.45–1.61)		0.99 (0.93–1.05)	0.98 (0.92–1.05)

*Adjusted for other lung diseases and previous fracture, income, living with someone vs living alone, working vs not working, number of bed days in hospital in 1999, number of contacts to GP or specialist in 1999, and alcoholism.

†Adjusted for the variables in the table.

‡Also adjusted for the variables in the table and previous fracture, income, living with someone vs living alone, working vs not working, number of bed days in hospital in 1999, number of contacts to GP or specialist in 1999, and alcoholism.

drug types analyzed in this article most often are used in stable lung disease or in periods when the lung disease is in a stable phase. Oral corticosteroids are also often used to control episodes of worsening of a lung disease. The increase in fracture risk with the use of oral corticosteroids and inhaled short-acting β-agonists may thus in part be due to the underlying lung disease, patients with a high use of these drugs probably having poorer lung function than patients not receiving such drugs. The poorer lung function may be associated with bone loss and an increased risk of fractures through the mechanisms mentioned in the introduction to this article.[2,4] Oral corticosteroids may also have a number of detrimental effects on bone, which may lead to an increased fracture risk,[5] whereas the absorption of inhaled corticosteroids probably is too low to give major systemic effects.[10] However, the risk of bone fractures in asthma and COPD with a treatment with inhaled steroids is controversial and may be different with different molecules and/or severity of the disease.[26–30]

Inhaled corticosteroids at high doses were associated with a decrease in overall fracture risk (Table 3) and spine fractures (Table 5), while the risk of hip fractures seemed decreased with all doses of inhaled corticosteroids (Table 5). The reasons for this are not entirely clear. It may be a chance finding or represent unexplained confounding. One reason could be that patients treated with inhaled corticosteroids are in a more stable phase of the disease than patients receiving oral corticosteroids and other types of bronchodilators, and patients in a stable phase of the disease may have a lower risk of fractures.

The increase in fracture risk with low doses of oral β-agonists may be linked to the fact that these are initiated in patients with unstable disease, whereas the maintenance treatment is used in patients with stable lung disease. The fact that an increase in fracture risk was seen only with some but not all types of β-agonists also points against a pharmacologic effect of the β-agonists.

The same factors concerning severity of the loss of lung function may explain the differences in relative risk associated with asthma and other chronic lung diseases, the risk associated with asthma being smaller than for COPD. In asthma, most patients have intermittent attacks of wheezing and dyspnea, and lung function may often be maintained at near normal levels between attacks; whereas in COPD, lung function may be permanently decreased leading to a loss of BMD and an increased fracture risk.[2,4] However, other factors such as more smoking and lower body mass index in patients with COPD than in asthma may also contribute.

The decline in fracture risk with duration of lung disease is intriguing but may be related to the factors mentioned above. In early stages, the patients may be in an unstable phase with hospital

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Table 3—*Risk of Any Fracture Associated With Drugs for Lung Diseases Adjusted for Confounders Including Indices of Severity of Lung Disease (All Variables Mentioned in Table 4)

Variables	OR (95% CI)
Oral corticosteroids, mg/d	
< 2.50	1.02 (0.98–1.06)
2.50–7.59	1.29 (1.22–1.36)
≥ 7.50	1.79 (1.68–1.91)
Inhaled corticosteroids, DDD	
≤ 50	1.00 (0.95–1.06)
51–300	0.96 (0.91–1.02)
> 300	0.93 (0.87–0.99)
Inhaled short-acting β-agonist, DDD	
≤ 50	1.16 (1.12–1.20)
51–300	1.14 (1.08–1.20)
> 300	1.13 (1.07–1.19)
Inhaled LABA, DDD	
≤ 50	1.04 (0.95–1.13)
51–300	1.05 (0.97–1.14)
> 300	0.94 (0.86–1.02)
β-Agonist and corticosteroid inhaled combined, DDD	
≤ 50	0.81 (0.62–1.06)
51–300	0.94 (0.77–1.13)
> 300	0.77 (0.43–1.38)
β-Agonist and antimuscarinic substance inhaled combined, DDD	
≤ 50	1.07 (0.97–1.17)
51–300	1.02 (0.93–1.12)
> 300	1.04 (0.94–1.13)
Oral β-agonist, DDD	
≤ 5	1.18 (1.10–1.28)
6–15	0.98 (0.93–1.03)
> 15	1.00 (0.96–1.05)
Antimuscarinic substances inhaled, DDD	
≤ 50	1.05 (0.90–1.23)
51–300	1.07 (0.91–1.26)
> 300	1.00 (0.88–1.15)
Cromoglycate	
≤ 50	0.92 (0.70–1.20)
51–300	0.74 (0.48–1.15)
> 300	0.55 (0.27–1.10)
Leukotriene receptor antagonists, DDD	
≤ 50	1.00 (0.85–1.18)
51–300	0.99 (0.85–1.17)
> 300	1.10 (0.93–1.30)
Theophylline, DDD	
≤ 50	0.95 (0.84–1.07)
51–300	1.00 (0.88–1.13)
> 300	0.95 (0.87–1.04)

*The reference is no diagnosis of the kind in question or no use of the drug in question.

Table 4—*Risk of Any Fracture Associated With Underlying Disease Adjusted for Drugs (All Drugs Mentioned in Table 3)

Variables	OR (95% CI)
Bed days in hospital for asthma	
≤ 2	1.10 (1.01–1.21)
2.1–8	1.09 (1.00–1.18)
> 8	1.15 (1.06–1.26)
Bed days in hospital for COPD	
≤ 4	1.18 (1.09–1.28)
4.1–10	1.19 (1.08–1.31)
> 10	1.46 (1.36–1.57)
Bed days in hospital for emphysema	
≤ 4	1.28 (1.05–1.57)
4.1–10	1.19 (0.95–1.49)
> 10	1.40 (1.14–1.72)
Bed days in hospital for other chronic lung disease	
≤ 4	1.32 (0.97–1.78)
4.1–10	1.08 (0.76–1.52)
> 10	1.31 (0.97–1.77)
Contacts to GP or specialist in 1999	
1–7	1.17 (1.13–1.21)
8–18	1.29 (1.24–1.33)
≥ 19	1.54 (1.49–1.60)
Income (≥ 150.000 vs < 150.000 DKK)	0.97 (0.95–0.99)
Living with someone vs living alone	0.88 (0.86–0.89)
Working vs out of work	1.04 (1.02–1.06)
Prior fracture	2.72 (2.68–2.77)
Alcoholism	2.46 (2.38–2.54)

*The reference is no diagnosis of the kind in question or no use of the drug in question. DKK = Danish kroner (one US dollar is equal to approximately 6.5 Danish kroners).

admissions, courses of prednisolone, and wheezing, and perhaps an increased risk of falls due to hypoxia and perhaps also a period with increased bone resorption, and thus an increased fragility risk from weakening of trabecular structure. However, this needs further study. Patients with long-standing lung disease may have a decreased BMD from many reasons as mentioned in the introduction to this article, but this may not be associated with an increased risk of fractures from a decreased physical activity and thus a decreased risk of falls. Another perhaps more important factor behind why duration was not positively correlated to fracture risk may be that duration does not reflect severity of the disease as well as, *eg*, the number of bed days in hospital or the number of contacts to the GP. Mild cases may dominate among patients with long disease duration because patients with severe cases may have a high mortality rate and thus a shorter disease course than patients with mild disease. Furthermore, fractures are linked to mortality,[31] and patients with fractures and severe lung disease leading to fractures may thus have shorter disease duration than patients with mild disease.

The absence of an increase in fracture risk with cromoglycate is in accordance with prior studies[15–17] showing no difference in BMD from normal subjects, but these studies have been confounded by concomitant use of oral and inhaled corticosteroids. Leukotriene receptor antagonists did not seem to affect fracture risk, so any influence on bone turnover seems to be too marginal to influence fracture risk.

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Table 5—*Relative Risk of Osteoporotic Fractures Multiply Adjusted for the Confounders Mentioned in Table 6

Variables	Hip	Forearm	Spine
Oral corticosteroids, mg/d			
< 2.50	1.01 (0.91–1.12)	0.98 (0.88–1.08)	1.33 (1.10–1.61)
2.50–7.59	1.38 (1.23–1.56)	1.14 (0.99–1.32)	1.82 (1.43–2.32)
≥ 7.50	1.69 (1.47–1.95)	1.20 (1.00–1.44)	2.44 (2.84–3.25)
Inhaled corticosteroids, DDD			
≤ 50	0.79 (0.65–0.96)	0.96 (0.83–1.12)	1.09 (0.80–1.47)
51–300	0.79 (0.65–0.95)	0.97 (0.84–1.12)	0.99 (0.73–1.34)
> 300	0.72 (0.60–0.86)	0.92 (0.78–1.08)	0.61 (0.44–0.84)
Inhaled short-acting β-agonist, DDD			
≤ 50	1.01 (0.88–1.16)	1.01 (0.91–1.13)	1.23 (1.00–1.52)
51–300	1.05 (0.88–1.25)	1.09 (0.95–1.25)	1.12 (0.84–1.48)
> 300	1.20 (1.02–1.41)	1.07 (0.92–1.25)	1.41 (1.05–1.89)
Inhaled LABA, DDD			
≤ 50	0.71 (0.52–0.95)	1.01 (0.79–1.29)	1.40 (0.91–2.14)
51–300	0.69 (0.53–0.89)	1.09 (0.88–1.36)	1.15 (0.75–1.76)
> 300	0.85 (0.66–1.09)	0.99 (0.78–1.26)	0.88 (0.57–1.35)
β-Agonist and corticosteroid inhaled combined, DDD			
≤ 50	0.56 (0.24–1.33)	0.85 (0.41–1.78)	0.63 (0.11–3.52)
51–300	0.88 (0.50–1.54)	1.05 (0.65–1.70)	0.74 (0.30–1.83)
> 300	0.48 (0.05–5.00)	1.41 (0.45–4.47)	
β-Agonist and antimuscarinic substance inhaled combined, DDD			
≤ 50	1.13 (0.90–1.41)	1.02 (0.80–1.30)	1.18 (0.84–1.90)
51–300	1.12 (0.90–1.39)	0.84 (0.65–1.09)	0.74 (0.48–1.15)
> 300	1.22 (0.99–1.50)	0.80 (0.62–1.02)	0.61 (0.40–0.94)
Oral β-agonist, DDD			
≤ 5	1.01 (0.71–1.46)	1.01 (0.81–1.27)	0.99 (0.60–1.65)
6–15	0.78 (0.67–0.92)	0.94 (0.82–1.08)	1.14 (0.87–1.49)
> 15	1.05 (0.93–1.17)	1.02 (0.90–1.16)	1.13 (0.89–1.44)
Antimuscarinic substances inhaled, DDD			
≤ 50	1.05 (0.73–1.51)	1.41 (0.95–2.09)	1.58 (0.77–3.24)
51–300	0.73 (0.50–1.07)	1.11 (0.72–1.72)	1.16 (0.51–2.62)
> 300	0.99 (0.74–1.31)	1.09 (0.77–1.56)	0.84 (0.46–1.54)
Cromoglycate, DDD			
≤ 50	1.05 (0.45–2.48)	0.61 (0.28–1.32)	2.06 (0.67–6.32)
51–300	1.63 (0.53–5.06)	0.99 (0.36–2.72)	
> 300	0.91 (0.21–4.96)	0.27 (0.03–2.14)	
Leukotriene receptor antagonists, DDD			
≤ 50	1.25 (0.78–1.99)	1.05 (0.71–1.57)	1.07 (0.48–2.37)
51–300	1.46 (0.96–2.23)	0.69 (0.44–1.07)	1.90 (0.93–3.88)
> 300	1.28 (0.81–2.02)	1.20 (0.75–1.91)	1.09 (0.48–2.48)
Theophylline, DDD			
≤ 50	0.66 (0.48–0.91)	1.21 (0.90–1.64)	0.75 (0.40–1.38)
51–300	0.97 (0.73–1.28)	1.00 (0.73–1.38)	0.85 (0.48–1.49)
> 300	0.97 (0.81–1.17)	1.13 (0.90–1.41)	1.24 (0.82–1.87)

*Data are presented as OR (95% CI).

To date, most studies[6,8–10,26,32,33] with fractures as an end point come from epidemiologic analyses. However, in order to study the effects of covariates not covered in detail by the administrative databases, large-scale controlled clinical trials of long duration are needed. This would allow the analysis of the effects a randomized trial of various inhaled glucocorticosteroids and alterations of lung function in patients with various lung disorders. Our results on the effects of the underlying lung disease are in accordance with recent results by de Vries et al.[33]

Limitations to the Study

In this study, we adjusted for potential confounders including variables that included severity of the disease such as number of contacts to GP and days in hospital in the previous year. However, this may not completely have adjusted for the severity of the lung disease because we did not have data on lung function (such as peak flow, vital capacity, walking distance), and this is a major weakness of the study. However, at present it is not known if introduction of

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Table 6—*Risk of Osteoporotic Fracture Associated With Underlying Disease Adjusted for the Drugs Mentioned in Table 5**

Variables	Hip	Forearm	Spine
Bed days in hospital for asthma			
≤ 2	1.01 (0.72–1.42)	1.13 (0.88–1.44)	0.91 (0.56–1.46)
2.1–8	1.41 (1.07–1.85)	1.22 (0.97–1.53)	0.77 (0.46–1.27)
> 8	1.27 (1.00–1.62)	1.31 (1.04–1.65)	0.82 (0.52–1.29)
Bed days in hospital for COPD			
≤ 4	1.35 (1.12–1.64)	1.28 (1.05–1.56)	1.03 (0.69–1.55)
4.1–10	1.76 (1.45–2.14)	1.13 (0.88–1.45)	1.35 (0.87–2.09)
> 10	2.19 (1.89–2.54)	0.98 (0.80–1.20)	2.26 (1.61–3.17)
Bed days in hospital for emphysema			
≤ 4	1.31 (0.81–2.12)	0.44 (0.22–0.89)	1.23 (0.48–3.17)
4.1–10	1.45 (0.91–2.31)	1.15 (0.61–2.15)	2.33 (0.82–6.59)
> 10	1.19 (0.77–1.83)	0.88 (0.43–1.77)	0.89 (0.29–2.70)
Bed days in hospital for other chronic lung disease			
≤ 4	1.14 (0.57–2.30)	1.48 (0.65–3.36)	1.41 (0.40–4.98)
4.1–10	1.30 (0.60–2.81)	1.52 (0.54–4.27)	0.92 (0.16–5.29)
> 10	1.46 (0.77–2.75)	1.73 (0.78–3.86)	0.68 (0.16–2.91)
Contacts to GP or specialist in 1999, No.			
1–7	1.03 (0.90–1.18)	1.15 (1.05–1.26)	1.35 (1.09–1.67)
8–18	1.07 (0.94–1.22)	1.17 (1.07–1.29)	1.46 (1.18–1.81)
≥ 19	1.47 (1.30–1.67)	1.25 (1.14–1.37)	1.92 (1.56–2.36)
Income (≥ 150.000 vs < 150.000 DKK)	0.91 (0.86–0.97)	0.98 (0.93–1.03)	1.04 (0.94–1.15)
Living with someone vs living alone	0.88 (0.84–0.93)	0.90 (0.86–0.94)	0.93 (0.85–1.02)
Working vs out of work	0.67 (0.60–0.75)	1.00 (0.94–1.05)	0.99 (0.89–1.11)
Prior fracture	2.33 (2.22–2.45)	2.02 (1.93–2.12)	2.60 (2.38–2.85)
Alcoholism	4.13 (3.65–4.67)	2.40 (2.18–2.64)	2.68 (2.24–3.19)

*The reference is no diagnosis of the kind in question or no use of the drug in question. See Table 4 for expansion of abbreviation.

these parameters would improve estimates over the quasivariables currently used (number of bed days and number of contacts to the GP) because the diagnosis and the number of bed days may correlate with disease severity. Further research is thus needed. Another major weakness is that we did not have data on smoking because smoking is associated both with lung diseases and fracture risk.[34] However, as smoking is related to the occurrence of, *eg*, COPD and emphysema, introduction of smoking in addition to the diagnoses may lead to an overadjustment because smoking is a part of the cause of these diagnoses and thus not a true confounder. Adjustment for smoking would thus lead to attenuation of the risk associated with the diagnosis *per se* in favor of a risk associated with smoking. We also did not have access to data on oxygen therapy at home (long-term oxygen therapy). Furthermore, no clinical data were available on the degree of control of asthma. However, the association between asthma and fracture risk was weak, and introduction of further corrections would thus be less likely to affect the results significantly. We only had access to diagnoses made in hospital, and not diagnoses made by the GP, and this means that only the more severe cases are included in the analysis, which will tend to underestimate the risk associated with the lung diseases in question because patients with lung disease are compared to patients who supposedly do not have lung disease, but in fact some do.

In conclusion, inhaled and oral bronchodilators seem safe in terms of fracture risk, and the increase in fracture risk may to a higher degree be linked to the severity of the underlying lung disease for which the drugs are administered. COPD and emphysema seem to be associated with a higher increase in fracture risk than asthma.

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Fracture Risk in Patients With Chronic Lung Diseases Treated With Bronchodilator Drugs and Inhaled and Oral Corticosteroids *

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