Adverse effects of oral corticosteroids in relation to dose in patients with lung disease

L J Walsh, C A Wong, J Oborne, S Cooper, S A Lewis, M Pringle, R Hubbard, A E Tattersfield

Abstract

***Background*—The adverse effects of oral corticosteroids are widely recognised but there are few quantitative data on which to base advice to patients. In a two part cross sectional study we compared adverse effects in patients with lung disease taking oral corticosteroids and control subjects and related the adverse effects to corticosteroid dose in the patient group.**

***Methods*—Data on oral corticosteroid use, lifestyle, fractures, and other possible adverse effects were collected by questionnaire and compared between a community based cohort of patients taking continuous or frequent intermittent oral corticosteroids for asthma, chronic obstructive pulmonary disease, or alveolitis and age and sex matched control subjects. Dose related effects were explored in the corticosteroid group using cumulative dose quartiles and multiple logistic regression.**

***Results*—A total of 367 patients (≥50 years, 48% female) and 734 control subjects completed the questionnaire. The cumulative incidence of fractures since the time of diagnosis was 23% for patients taking oral corticosteroids and 15% in the control group (odds ratio (OR) 1.8; 95% confidence interval (CI) 1.3 to 2.6). Patients were more likely to have had a fracture of the vertebrae (OR 10; 95% CI 2.9 to 34), hip (OR 6; 95% CI 1.2 to 30), and ribs or sternum (OR 3.2, 95% CI 1.6 to 6.6) than control subjects. They also reported a significant increase in cataracts, use of antacids, muscle weakness, back pain, bruising, oral candidiasis, and having fewer teeth. The effects of oral corticosteroids were dose related: the odds ratio for patients in the highest compared with the lowest cumulative dose quartile (median prednisolone dose 61 g versus 5 g) ranged from 2 for all fractures to 9 for vertebral fractures and bruising.**

***Conclusions*—By quantifying the morbidity associated with the use of oral corticosteroids, this study should help to rationalise their long term use.**

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Keywords: oral corticosteroids; dosage; adverse effects; fractures; osteoporosis

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Oral corticosteroids are the most effective treatment available for many medical conditions including severe chronic asthma. Following their introduction 50 years ago their use has escalated and, despite the widespread use of inhaled corticosteroids, some 50 000 patients with asthma and chronic obstructive pulmonary disease (COPD) in the UK take oral corticosteroids regularly.[1] Adverse effects such as osteoporosis, cataract, and muscle weakness are widely recognised and have considerable public health implications. They are also of concern to patients who need to balance the beneficial and adverse consequences of corticosteroid therapy. One difficulty when trying to address both public health issues and patient concerns is the lack of quantitative data on which to base advice.

Osteoporosis is probably the adverse effect of greatest concern and one that is amenable to prophylactic intervention. Most studies that have attempted to assess fracture risk in patients taking oral corticosteroids have been small or confounded by the underlying disease such as rheumatoid arthritis.[2–5] In a recent study the risk of hip fracture over 4 years was doubled in patients taking oral corticosteroids compared with a control population.[6] There are, however, no data on the risk of fracture or other adverse effects in relation to dose or duration of oral corticosteroid therapy after allowing for confounding influences. We have addressed this by using computerised general practice records to identify patients over the age of 50 who are taking oral corticosteroids for obstructive airways disease or alveolitis, two conditions that do not cause symptoms that could easily be attributed to oral corticosteroids. The first study provides information on the prevalence of fracture and other adverse effects compared with an age and sex matched control population. The second looks at how the incidence of fractures and other adverse effects relate to cumulative prednisolone dose.

Methods

SUBJECTS

Fifty one general practices close to Nottingham and with a computerised record of drug prescriptions for at least 1 year participated in the study. Patients with asthma, COPD, and fibrosing alveolitis who were taking oral corticosteroids were identified from the computerised drug record and the paper medical record was used to provide further details. Age and sex matched control subjects were identified by reviewing the drug history of subjects of the same sex immediately above and below the patient on a list of practice patients ranked by date of birth.

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ENTRY CRITERIA

Men and women aged 50 years or more with a diagnosis of asthma, COPD, or fibrosing alveolitis were included if they required either (a) continuous oral corticosteroids, defined as daily or alternate day oral corticosteroid therapy for at least the last 6 months or (b) frequent intermittent courses of oral corticosteroids, defined as a mean daily dose of 5 mg prednisolone (or equivalent dose of other corticosteroid) over the previous 6 months. Patients receiving oral corticosteroids for other conditions were excluded.

Control subjects had never had oral corticosteroid treatment or a diagnosis or treatment for lung disease. Patients and control subjects were excluded if they had a metabolic disease known to affect bone metabolism such as thyrotoxicosis or were not well enough to take part.

STUDY PROTOCOL

A questionnaire with an explanation of the study and a personal letter signed by the general practitioner was sent to each patient and three age and sex matched control subjects. Subjects were asked to complete the questionnaire or contact us if help was needed. If no reply was received after 3 weeks the patient was contacted by telephone and assistance offered. If two control subjects had not replied after a repeat mailing further control subjects were approached; if all three replied the first two identified were used.

STUDY 1: QUESTIONNAIRE STUDY

The questionnaire asked for details, including duration or timing, of the main end points: fractures, back pain, bruising, muscle weakness, the presence and condition of teeth, and a diagnosis of cataract, diabetes, hypertension, herpes zoster, and oral thrush. All fractures except those of the skull, facial bones, fingers, and toes were included. Information from the control subjects was obtained for the same time period as their matched patient which was since the patient's diagnosis was made or since 1950, when oral corticosteroids were first used, whichever was later. Muscle weakness was assessed by asking subjects whether they had difficulty getting out of a chair or climbing stairs compared with others of their own age. The use of antacids, H_2-receptor antagonists, and proton pump inhibitors was used as a measure of indigestion. Subjects were asked to obtain a measurement of their current weight and height without shoes on; height loss (cm) was assessed from the patients reported height at age 25 years.

The questionnaire also asked for information on lifetime cigarette consumption in pack years, alcohol intake (classified as <10, 10–30 or >30 units/week), weekly consumption of milk, cheese and yoghurt to estimate mean daily calcium intake (mg/day) using dietary tables,[7] age at menopause (age at last menstrual period or, for premenopausal patients having a hysterectomy but no oophorectomy, when menopausal symptoms commenced), and exercise determined from regular sporting activity between ages 15 and 25 years and at present on a five point scale (1 = none to 5 = more than three times per week). Patients were also asked to grade their most strenuous daily activity as light, moderate, heavy, or very heavy. Drug use, including hormone replacement therapy, vitamin D, calcium supplements, thiazide diuretics, bisphosphonates, other treatment for osteoporosis, and any family history of osteoporosis or height loss was recorded.

The general practice computerised and written records were studied for subjects in both groups to confirm the presence or absence of a respiratory diagnosis and use of corticosteroids.

STUDY 2: DOSE RESPONSE STUDY

The relationship between oral corticosteroid dose and fracture in the past 30 years, cataract ever, current bruising, and muscle weakness was assessed in the patients taking oral corticosteroids. The total cumulative dose and duration of oral corticosteroid therapy was estimated from the questionnaire and corroborated against the general practice record, without knowledge of the main outcome measures. The questionnaire provided information on the corticosteroid used, daily dose, duration of treatment, mean number of booster courses per year, and the dose prescribed for a typical course. The computerised record provided information on daily dose, number of tablets prescribed, dose per tablet, and duration of treatment while the paper record provided data prior to the computer record.

For the primary analysis we calculated the patient's total lifetime dose as the total dose of prednisolone (g) or equivalent taken at any time—that is, continuous plus previous courses. Oral corticosteroids other than prednisolone were converted to prednisolone equivalent doses.[8] In a secondary analysis we looked at the relation between duration of treatment (total time that continuous or frequent intermittent corticosteroids had been taken) and mean daily dose during the 6 months before the questionnaire on adverse effects (including any additional treatment for exacerbations). The use of inhaled corticosteroids was measured as a total lifetime dose (mg).

ANALYSIS OF DATA

Demographic, lifestyle, and all outcome measures were compared between the corticosteroid and matched control groups. The independent effect of corticosteroids on adverse effects was assessed using conditional logistic regression with appropriate interaction terms to assess any modifying effect of sex. Odds ratios were calculated to give an estimate of the rate ratio.[9]

For the dose response study patients taking oral corticosteroids were grouped into quartiles according to their total cumulative dose of prednisolone. Significant adverse effects of interest identified in study 1 were then compared in the different quartiles using multiple logistic regression analysis; p values refer to a test of linear trend in odds ratios across quartiles. The analysis controlled for sex, age

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Table 1 Demographic data for patients with obstructive airways disease or alveolitis taking oral corticosteroids and control subjects

	n	*Corticosteroid patients*	*n*	*Control subjects*	*p value*
Women					
Age (years)	177	68.2 (9.5)	354	68.3 (9.5)	
Body mass index (kg/m^2)	171	26.5 (6.9)	335	25.6 (4.0)	NS
Age at menopause	167	47.0 (4.9)	292	48.2 (4.3)	0.01
HRT (number of years)	36	2.7 (3.0)	82	4.2 (3.9)	NS
Smoking (pack/years)	112	20 (0.05–114)*	179	14 (0.01–104)*	0.003
Calcium from dairy produce (mg)	172	631 (25–1198)*	354	626 (9–1295)*	NS
Bisphosphonate/calcitonin	20		4		<0.001
Calcium supplement	25		21		0.01
Men					
Age (years)	190	69.6 (9.1)	380	69.8 (9.1)	
Body mass index (kg/m^2)	181	25.6 (6.0)	364	26.0 (3.5)	NS
Smoking (pack/years)	164	29.9 (0.2–150)*	293	20 (0.1–255)*	0.009
Calcium from dairy produce (mg)	183	614 (25–1070)*	380	626 (9–1241)*	NS
Bisphosphonate/calcitonin	4		1		0.12
Calcium supplement	13		6		0.005

Values are mean (SD) or *median (range).
HRT = hormone replacement therapy.
All p values obtained by conditional logistic regression.

(four levels), body mass index (three levels), cumulative inhaled steroid dose (four levels), cigarette consumption (none, ⩽ 20, >20 pack years), alcohol intake (two levels), calcium intake, age at menopause, exercise currently and at age 15–20 years (three levels), and daily activity (two levels). The effect of duration of corticosteroid use and the mean dose of prednisolone over the previous 6 months was analysed using quartiles in a similar way.

Data were analysed using the SPSS 8.0 for Windows statistical program (SPSS Inc, Chicago, Illinois, USA) and EGRET (SERC, Seattle, USA).

Results

We identified 452 patients taking oral corticosteroids who fulfilled the entry criteria; 367 (81%) completed the questionnaire of whom 48% were female. Of the 85 who did not respond, 15 were too unwell, one had moved, and the remainder did not wish to participate. Two control subjects were identified from the same practice for each patient; the response rate for the control subjects was 61% but this will be a conservative estimate as no allowance was made for patients who had died or moved (21% of patients in a comparable study in Nottingham[10]).

Among the 367 patients taking oral corticosteroids 162 (44%) had a recorded diagnosis of asthma, 111 (30%) had asthma and COPD, 82 (22%) had COPD alone, and 12 (3%) had fibrosing alveolitis. For most patients (98%) the corticosteroid taken was prednisolone with a median total lifetime dose of 16.3 g (range 1.1–186 g) over a median of 5.5 years (range 0.5–46 years). Women had a higher median cumulative lifetime dose than men (20 g *v* 15.3 g) and a higher median duration of steroid use (6.4 years *v* 4.5 years). A quarter of the patients had taken frequent intermittent oral corticosteroids in the previous 6 months and 89% were taking an inhaled steroid regularly.

Table 2 Fractures and other adverse effects in patients taking oral corticosteroids compared with the control population

	Steroid patients (%)	*Control group (%)*	*No of case control sets*	*Unadjusted odds ratio (95% CI)*	*p value**
Fractures					
Any "osteoporotic" fracture	23.2	14.7	367	1.8 (1.3 to 2.6)	<0.001
2 or more fractures	7.4	3.1	367	2.5 (1.4 to 4.4)	0.003
Vertebrae	4.1	0.4	367	10.0 (2.9 to 34.5)	<0.001
Hip	1.6	0.3	367	6.0 (1.2 to 29.7)	0.03
Ribs/sternum	5.4	1.8	367	3.2 (1.6 to 6.6)	0.001
Wrist	5.7	6.1	367	0.9 (0.5 to 1.6)	0.8
Upper limb (not wrist)	4.4	2.0	367	2.1 (1.1 to 4.3)	0.04
Lower limb	5.7	4.5	367	1.3 (0.7 to 2.3)	0.4
Clavicle/scapula	1.4	1.4	367	1.0 (0.3 to 2.9)	1.0
Symptoms					
Back pain in past year	54.3	48.2	362	1.3 (1 to 1.7)	0.05
Bruising	72.9	10.9	362	21.9 (13.9 to 34.5)	<0.001
Muscle weakness	59.8	19.3	360	6.7 (4.8 to 9.3)	<0.001
Height loss of >2.5cm (since age 25)	37.6	26.3	367	1.7 (1.3 to 2.2)	<0.001
Diagnosis of:					
Cataracts	18.4	8.6	365	2.6 (1.8 to 3.9)	<0.001
Diabetes	6.5	4.6	364	1.4 (0.8 to 2.5)	0.2
Hypertension	17.8	23.5	356	0.7 (0.5 to 1.0)	0.05
Oral candidiasis	29.7	2.7	364	15.5 (8.7 to 27.6)	<0.001
Use of H_2 antagonists	22.6	7.8	367	3.5 (2.4 to 5.1)	<0.001
Shingles (since respiratory diagnosis)	12.5	9.4	367	1.4 (0.94 to 2.1)	0.1
Teeth (none)	51.2	38.8	363	1.8 (1.4 to 2.4)	<0.001

*Obtained by conditional logistic regression.

STUDY 1: COMPARISON OF CORTICOSTEROID AND CONTROL SUBJECTS

There was no significant difference between the patients and their age and sex matched controls with regard to race (>98% white), body mass index, calcium intake, a family history of height reduction or osteoporosis, the use of thiazide diuretics, and hormone replacement therapy in women (table 1). Patients on corticosteroids were more likely to have received a bisphosphonate or calcium supplements than control subjects (17% *v* 4%) and the women had a slightly earlier age at menopause (47 *v* 48 years).

Patients taking oral corticosteroids were more likely to have smoked than control subjects (75% *v* 64%) and to have smoked more heavily but there was no difference in the number of current smokers (cases 16.2%, controls 17.9%) nor in alcohol intake. Current regular exercise and the most strenuous daily activity undertaken were lower in the corticosteroid population (p<0.001) although sporting activity was similar at age 15–25 years.

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Table 3 Demographic data for the corticosteroid quartiles (total cumulative dose of prednisolone)

	Corticosteroid quartile			
	1	*2*	*3*	*4*
Mean (SD) demographic data				
Age	71 (9.0)	68 (9.4)	71 (8.7)	67 (9.4)
Women (%)	47	39	47	60
Age at menopause	46 (4.5)	48 (4.7)	47 (5.5)	47 (4.7)
Dose of prednisolone				
Median cumulative (g)	5.1	11.7	23.6	60.6
Range	1.1–7.7	7.8–16.3	16.4–37.4	37.6–186

Fracture risk

Patients taking oral corticosteroids had had significantly more fractures than the control group (odds ratio 1.8) and were more likely to have had two or more fractures (OR 2.5) and fractures of the vertebrae (OR 10), hip (OR 6), and ribs or sternum (OR 3.2; table 2). Corticosteroid use did not affect the prevalence of fractures of the wrist, clavicle, or scapula. Adjustment for the differences between the steroid and control group in smoking, current regular exercise, and most strenuous daily activity had little effect on the size of the odds ratios (adjusted OR for total fractures 1.75, 95% CI 1.1 to 2.7). The only modifying effect of sex was in relation to having two or more fractures ($p_{interaction} = 0.03$) which was increased in women (12% *v* 4%) but not in men taking corticosteroids. Height loss of 2.5 cm or more was more common in women taking corticosteroids (45% *v* 28%) but not in men.

Other adverse effects

The problems reported most frequently by patients taking oral corticosteroids include bruising (73%), muscle weakness (60%), back pain (54%), oral candidiasis (30%), indigestion (23%), and a diagnosis of cataract (18%). All occurred significantly more frequently in the patients on oral corticosteroids than in the control population with odds ratios ranging from 1.3 for back pain to 21 for bruising (table 2). Diagnoses of diabetes and herpes zoster were slightly more common in the corticosteroid group but the differences from control were not significant. More control subjects reported a diagnosis of hypertension. Half the patients taking oral corticosteroids had no natural teeth compared with 39% in the control population (p<0.001) and, of those with teeth, twice as many reported that they were in poor condition.

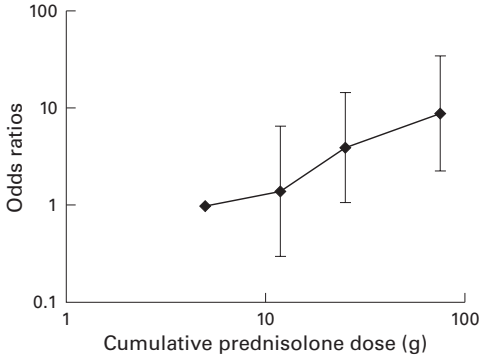

Figure 1 Adjusted odds ratios for vertebral fractures for the highest three cumulative prednisolone dose quartiles compared with the lowest dose quartile (plus 95% confidence intervals); n = 4, 4, 12 and 15 vertebral fractures per quartile, respectively.

STUDY 2: ORAL CORTICOSTEROID DOSE RESPONSE STUDY

Demographic data for the patients according to quartiles based on their cumulative dose of prednisolone are shown in table 3. The dose of prednisolone approximately doubled for each successive quartile with a slightly greater increase in the highest quartile. There was little difference in mean age between quartiles but there were more women in the highest dose quartile.

After allowing for confounding variables there was a dose related increase in all fractures, vertebral fractures, and two or more fractures. The odds ratio for risk of fracture in the highest compared with the lowest quartile ranged from 2.2 for any fracture to 9 for vertebral fractures (table 4, fig 1). All hip fractures occurred in the two highest dose quartiles.

There was also a highly significant dose relationship between oral corticosteroid use and cataract, bruising, and muscle weakness after allowing for confounding variables with odds ratios for the highest compared with the lowest quartile of 3 for cataract and muscle weakness

Table 4 Relationship of 30 year cumulative incidence of fracture, cataract, ever and current bruising, and muscle weakness with total cumulative corticosteroid dose quartiles

		Corticosteroid quartile							
		1	*2*		*3*		*4*		
	Analysis	*OR*	*OR*	*95%CI*	*OR*	*95% CI*	*OR*	*95% CI*	*p trend*
All fracture	UV	1.0	1.5		1.8		1.9		
	MV	1.0	1.96	0.95 to 4.0	2.13	1.04 to 4.4	2.22	1.04 to 4.8	0.04
Vertebrae	UV	1.0	1.0		3.3		4.4		
	MV	1.0	1.4	0.31 to 6.7	4	1.06 to 15	9.2	2.4 to 36	<0.001
Ribs/sternum	UV	1.0	5.6		5.5		3.8		
	MV	1.0	6.3	1.23 to 33	5.9	1.14 to 31	5.4	0.94 to 31	0.1
2 or more fractures	UV	1.0	1.2		1.8		2.5		
	MV	1.0	1.9	0.61 to 5.7	2.4	0.83 to 7.1	4.1	1.4 to 12	<0.01
Cataract	UV	1.0	0.7		2		1.6		
	MV	1.0	0.9	0.36 to 2.3	2.5	1.1 to 5.6	3.1	1.3 to 7.5	0.002
Bruising	UV	1.0	1.5		2.8		4.2		
	MV	1.0	2.2	1.03 to 4.6	3.9	1.7 to 8.6	9.4	3.6 to 25	<0.001
Muscle weakness	UV	1.0	1.3		1.9		2.1		
	MV	1.0	1.5	0.79 to 3	2.5	1.2 to 5	3.3	1.5 to 7	<0.001

Odds ratios are given using multiple logistic regression analysis in relation to the first quartile in a univariate (UV) and multivariate (MV) analysis with 95% confidence intervals for the latter.

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and 9 for bruising. There was no significant difference in any outcome measure between patients taking continuous oral corticosteroids and those receiving frequent intermittent courses after allowing for total cumulative prednisolone dose and other variables.

The effects of duration of oral corticosteroid use and mean dose over the previous 6 months were less marked than the effects of cumulative oral corticosteroid dose. Nevertheless, duration of treatment was significantly related to vertebral fracture (adjusted OR for highest *v* lowest quartile = 4.3) and bruising (OR 4.7) whereas mean dose over the previous 6 months was related to all fractures (OR 2.3), vertebral fracture (OR 5.0), two or more fractures (OR 5.6), bruising (OR 2.0), and cataract (OR 2.6).

Discussion

Oral corticosteroids are of great benefit in many conditions and can be life saving. Adverse effects were noted shortly after their introduction[11–13] but the extent and magnitude of these adverse effects in relation to dose are not well documented. We have looked at adverse effects in a large community population of patients compared with control subjects and have related the incidence of adverse effects to the total dose of oral corticosteroid. Our main end point was the cumulative incidence of fractures since osteoporosis and the associated risk of fracture is a major concern with oral corticosteroid use and has considerable public health implications.[14]

We compared adverse effects in each patient with two age and sex matched control subjects from the same general practice over the same time period. Our questionnaire response rate for both cases and controls was reasonable, considering the delays that arise in updating general practice lists. The case response rate exceeded that for the control subjects as expected, since the steroid group was identified from recent prescriptions. It is possible that the lower response rate in the control subjects led to an overestimate of fracture rate in this group, since subjects with a fracture may be more likely to respond to the questionnaire than those without. This would cause the impact of oral corticosteroids on fracture to be underestimated. On the other hand, we cannot exclude a possible effect of recall bias on some end points since patients taking oral corticosteroids may be aware of potential adverse effects and more likely to report bruising and back pain, and antacids may be prescribed more readily. It seems unlikely, however, that this bias will extend to the reporting of major events such as fracture and cataract, with the possible exception of vertebral fractures. In the event, the size of the effects we observed for the main end points was large and consistent between the case-control and dose response studies.

The first study confirmed the increased risk of fracture in patients taking oral corticosteroids seen in previous studies.[2–6] The greatest effect was seen with vertebral fracture where the odds ratio was 10 compared with the control subjects. These figures are higher than most previous estimates but comparison between studies is difficult due to different methods of ascertainment of vertebral fractures, the small size of previous studies, and confounding by diseases such as rheumatoid arthritis which affect fracture risk independently.[4] Our figures will underestimate the true incidence of vertebral fracture since they refer to the number of patients who were aware that they had had a vertebral fracture and did not assess the number of vertebral fractures that a patient might have had. Although the major effect of corticosteroids is on trabecular bone, hip fracture was increased among the patients which is in keeping with previous findings.[4 6 15] The increased risk of fractures with oral corticosteroids was seen in both sexes although loss of height was greater in women.

In study 2 we analysed the cumulative incidence of fractures in the last 30 years to ensure comparable time periods of observation for each dose quartile while minimising the number related to sport and accidents in young adults. The risk of having a fracture was closely related to dose and again the largest effect was seen with vertebral fractures where the odds ratio for patients in the highest dose quartile compared with those in the lowest quartile was 9. The dose related effects of steroids on fracture may be an underestimate since some fractures would have occurred prior to corticosteroid use and the steroid dose refers to the total dose before and after the fracture occurred. Most of the corticosteroid and fracture data were derived from the questionnaire and computerised records so the opportunity for observer bias was minimal. The study had limited power to look at the shape of the dose response relation to oral corticosteroid use but there was no evidence of a plateauing of effect with higher doses.

A wide range of other adverse effects of oral corticosteroids has been documented previously although the incidence of specific complications has varied considerably[16–18] because of small numbers and differences in the patients studied. Our study confirmed the association of oral corticosteroids with bruising, muscle weakness, oral candidiasis, use of antacids, and cataracts. We also found that patients taking oral corticosteroids were more likely to have no natural teeth or teeth in poor condition, although whether this is due to oral corticosteroids or to the concomitant use of inhaled drugs by these patients is uncertain.[19 20] The outcome measures which showed the largest difference between patients and control subjects in study 1 (vertebral fractures and bruising) also showed the greatest dose related effects in study 2.

This study has shown substantial differences in the risk of fractures and other adverse effects between a community based population of patients with lung disease taking oral corticosteroids and an individually matched control group. The adverse effects were strongly related to the total cumulative dose of prednisolone taken. Many of these adverse effects cause considerable morbidity to patients. The extent to which the adverse effects could have

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been avoided or prevented by lower doses of prednisolone or by preventative therapy is uncertain, but the low incidence of treatment to prevent osteoporosis is notable. Quantifying the morbidity from oral corticosteroids in the community and knowing the extent to which their adverse effects are dose related should encourage policies to prevent adverse effects and help rational prescribing of these valuable and widely used drugs.

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