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Dose–response relationship for risk of non-vertebral fracture with inhaled corticosteroids

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Summary

Objective To determine the strength of association between the dose of inhaled corticosteroids (ICS) and risk of non-vertebral fracture in adults.

Methods A systematic review and meta-analysis of case–control studies of non-vertebral fractures in adults, in which at least two doses of ICS were reported as the dose of beclomethasone dipropionate (BDP) or equivalent.

Results Five case–control studies were identified, with a total of 43 783 cases and 259 936 controls. There was an association between the risk of non-vertebral fracture and increasing dose of BDP. The random-effects odds ratio of relative risk for a non-vertebral fracture was 1.12 (95% confidence interval 1.00–1.26) per 1000 µg increase in the daily dose of BDP or equivalent.

Conclusion In older adults, the relative risk of non-vertebral fractures increases by about 12% for each 1000 µg/day increase in the dose of BDP or equivalent. The magnitude of this risk was considerably less than other common risk factors for fracture in the older adult.

Keywords adults, asthma, dose–response, fracture, inhaled corticosteroids

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Introduction

The clinical use of inhaled corticosteroids (ICS) in the treatment of asthma and chronic obstructive pulmonary disease (COPD) has been influenced by concerns regarding the systemic adverse effects including the risk of fracture. Several different methods have been utilized to assess risk of fracture with ICS use, including biochemical markers of bone turnover, and bone mineral density (BMD). However, short-term changes in biochemical markers such as alkaline phosphatase, osteocalcin, hydroxyproline, pro-collagen peptides and pyridinium crosslinks are of uncertain clinical relevance and have not been shown to predict the risk of fracture [1–3]. Likewise, there are limitations with the use of BMD measurements due to the evidence that the adverse effects of corticosteroids are primarily a consequence of disruption of collagen structure and bone architecture, rather than demineralization [4, 5]. Indeed, bone density does not measure the predominant properties that determine bone strength, namely its material composition and its structural design [6–8]. Furthermore, the correlation between steroid use and reduction in BMD

is poor and does not account for the magnitude of fracture risk associated with steroid therapy [4, 9, 10].

A more clinically relevant approach for determining the adverse effects of ICS on bone is to directly assess the strength of association for the risk of fracture and ICS dose. We have recently used a similar approach in determining the effects of ICS on adrenal function by directly assessing the dose–response relationship of ICS in causing the clinically relevant outcome of abnormal adrenal function [11]. In the current study, we undertook a systematic review and meta-analysis of case–control studies that investigated the strength of association of ICS therapy and risk of non-vertebral fracture.

Methods

A search of Medline was conducted from January 1950 to January 2007 and of EMBASE from January 1988 to January 2007. On Medline, studies were searched using a combination of the keywords ‘inhaled corticosteroids’ and ‘fractures’. No relevant studies published in languages other

than English were found on Medline or EMBASE. Finally, the reference lists of relevant studies were examined.

Inclusion criteria

Two authors (K. P. and K. J.) examined each paper's title and abstract and the full paper, if necessary. Studies that met the following criteria were included in the meta-analysis:

- A case-control study of non-vertebral fracture and the use of ICS.
- At least two doses of ICS reported predominantly as the equivalent dose of beclomethasone dipropionate (BDP) per day.
- The number of cases and controls using each dose of ICS was reported.
- The study reported odds ratios for the risk of non-vertebral fracture for each ICS dose compared with no use, adjusted for potential confounding variables, together with confidence intervals (CIs).

Statistical methods

For summarized dose-response data, there were two issues that needed to be addressed in the analysis. Firstly, where each dose level was compared with subjects who did not use ICS, the odds ratios reported within each trial were not independent measurements of association, as would be the case in a meta-analysis of the outcome of dose-response in a randomized clinical trial. Within each trial, the odds ratios for association are correlated with each other as they share the same 'non-user' group. Secondly, it is usual that the odds ratios for different doses are presented after adjustment for potential confounding variables. To take both these into account, the method of Greenland and Longnecker [12] was used, which estimates the correlation of odds ratios within each trial and also generates model-dependent cell totals, i.e. adjusted for confounding variables, to allow calculation of appropriate measurements of variance. The method gives an estimate of the slope coefficient relating the logarithm of the odds of an event to increasing doses, together with a variance estimate. This estimate also has the advantage that it provides a more powerful test for association than that based on comparisons of individual dose bands with non-use of ICS. These slope coefficients can then be pooled by an inverse weighting variance method, including tests for homogeneity, the I^2 statistics, and displayed in a forest plot [13, 14]. If heterogeneity was detected, our pre-specified plan was to attempt, should there be sufficient studies, a meta-regression to determine the sources of heterogeneity, or failing this to present a random-effects estimate to more correctly express uncertainty about the

magnitude of association. In the event, there were insufficient consistently recorded study-level characteristics and too few studies to attempt meta-regression.

To determine the dose used in our analysis, the midpoint of each dose range in the individual papers was calculated, with a minimum dose of zero. The maximum dose was derived by the addition of 500 µg to the top of the dose range cited in each paper, except for those papers where the maximum dose was given as > 1600 µg where 200 µg was added. ICS use was recorded as average daily dose based on prescription history, as specified in the identified papers. The mean duration of the prescription history was recorded.

The magnitude of the association expressed as a relative risk associated with ICS therapy was compared with that of other commonly recognized risk factors, reported from the study of Hubbard *et al.* [15] derived from the United Kingdom General Practice Research Database (UKGPRD). A simple plot of the estimated risks by dose of ICS as well as our pooled estimate is presented. Although our pooled estimate is presented on the same plot, the implied use of a 'zero' intercept is so that our pooled estimate of risk is on the same scale as that of the studies used to provide this estimate. SAS Version 9.1 and S-Plus Version 6.1 were used.

Results

The flow of study identification and inclusion and exclusion are shown in Fig. 1. Five studies were identified as

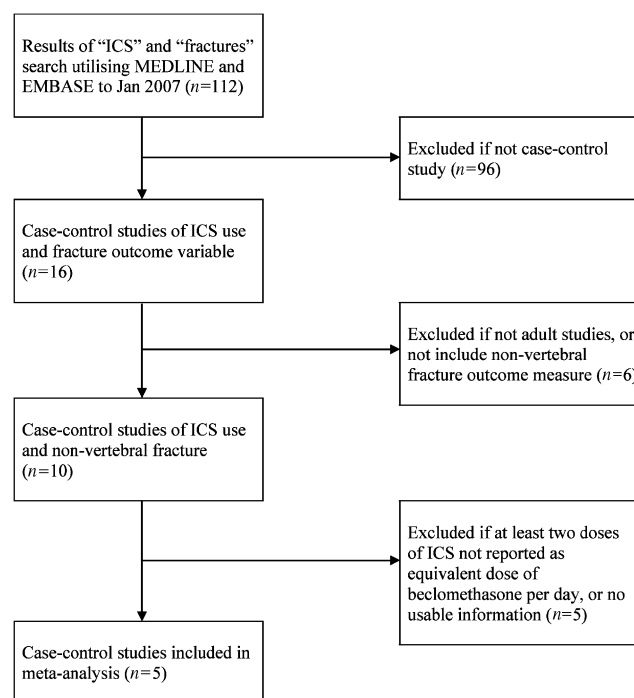


Fig. 1. Flow of study selection.

suitable for meta-analysis, as summarized in Table 1 [15–19]. In four of the studies [16–19], the ICS doses were presented as BDP equivalence. The study by Hubbard et al. [15] reported that 98% of ICS use was as beclomethasone and budesonide, and so we chose to include these data although 2% of the prescriptions were for fluticasone, and were not recoded to BDP equivalents. The dose ranges, number of subjects in the case and control groups using

Table 1. Characteristics of studies included in meta-analysis

Study	Population	Design	Adjustments
Hubbard et al. [15]	UKGPRD Hip fracture Mean age 79 years Mean prescription history: 2.7 years	1 : 2 matched case-control study	Use of oral corticosteroids
Suissa et al. [16]	Health insurance database Canada Hip or upper extremity fracture Mean age 81 years Mean prescription history: 4 years	1 : many matched case-control study	Age, sex, prescriptions of a variety of drugs, cumulative dose of oral corticosteroids
Lee and Weiss [17]	US Veterans' Association database of COPD subjects Non-vertebral fractures Mean age 63 years Mean prescription history: 1.75 years	1 : 4 matched case-control study	Co-morbidities, medications, annual hospitalizations and oral corticosteroid use
Johannes et al. [18]	US healthcare database, COPD subjects Non-vertebral fractures Mean age not given, 10% aged over 65 years Mean prescription history: 1 year	1 : 10 matched case-control study	Demographics, medical conditions, medication use including oral corticosteroid use and health utilization for underlying respiratory disease
de Vries et al. [19]	UKGPRD Any fracture selected, hip fracture data used Mean age not given for hip fracture subjects Mean prescription history: 2.2 years	1 : 1 matched case-control study	General risk factors, smoking status, body mass index, duration of enrolment in database, indicators of OAD severity, exposure to bronchodilators, in subjects never exposed to oral corticosteroids

COPD, chronic obstructive pulmonary disease; UKGPRD, United Kingdom General Practice Research Database.

these doses and the adjusted odds ratios for risk of non-vertebral fracture for all studies included are shown in Table 2. Other studies were excluded, primarily if no dose-response data were presented [20–24], or if they were not case-control studies [25, 26].

There was an increase in the risk of non-vertebral fracture with increasing doses of ICS. The estimates of the slope coefficients relating dose to the risk of non-vertebral fracture expressed as a log odds ratio, and the odds ratio, per 1000 µg increase in dose, are shown for the individual studies in Table 3. The fixed-effects odds ratio of risk for a non-vertebral fracture was 1.08 (95% CI 1.03–1.12) per 1000 µg increase in the daily dose of BDP or equivalent (Table 4). The homogeneity statistic, χ^2 statistic 18.8 on 4 df, $P < 0.001$, and I^2 statistic suggested that the variability in the study estimates was greater than that assumed by a fixed-effects model. The random-effects odds ratio of risk for a non-vertebral fracture was 1.12 (95% CI 1.00–1.26) per 1000 µg increase in dose.

With only five studies included in the meta-analysis, it was not possible to assess study-level covariates that

Table 2. Dose-response relationship of non-vertebral fracture with ICS use

Study	Mean daily dose (µg)*	Case (N)	Control (N)	Adjusted odds ratio (95% CI)
Hubbard et al. [15]	None	15114	28083	Reference level
	< 100	335	555	1.06 (0.93–1.22)
	101–200	164	267	1.09 (0.89–1.32)
	201–400	289	411	1.23 (1.06–1.44)
	401–800	286	394	1.27 (1.08–1.48)
	801–1600	128	156	1.39 (1.09–1.76)
	1600+	25	23	1.87 (1.06–3.33)
Suissa et al. [16]	None	3951	81116	Reference level
	0–500	3255	66699	0.94 (0.89–0.99)
	500–1000	1443	26978	0.99 (0.92–1.06)
	1000–1500	643	11450	1.05 (0.95–1.16)
	1500–2000	256	4181	1.08 (0.93–1.25)
	2000+	76	1198	1.11 (0.86–1.43)
Lee and Weiss [17]	None	1343	5309	Reference level
	< 300	108	526	0.83 (0.66–1.04)
	300–699	149	626	0.96 (0.78–1.17)
	700+	108	356	1.20 (0.95–1.52)
Johannes et al. [18]	None	1106	11241	Reference level
	1–167	328	3202	0.97 (0.84–1.12)
	168–504	183	1879	0.93 (0.78–1.12)
	505–804	61	485	1.10 (0.82–1.47)
	804+	44	413	0.93 (0.66–1.30)
de Vries et al. [19]	None	13725	13920	Reference level
	1–400	188	139	1.01 (0.76–1.34)
	401–800	212	164	0.97 (0.74–1.28)
	801–1600	190	120	1.09 (0.81–1.48)
	1600+	73	45	1.18 (0.75–1.85)

*Mean daily dose of ICS, BDP or equivalent.

BDP, beclomethasone dipropionate; ICS, inhaled corticosteroids.

Table 3. Slope coefficients and odds ratios relating risk of non-vertebral fracture to ICS use per 1000 µg*

Study	Slope coefficient (variance)	Odds ratio (95% CI)
Hubbard et al. [15]	0.35 (4.9×10^{-4})	1.42 (1.24–1.63)
Suissa et al. [16]	0.04 (6.4×10^{-4})	1.04 (0.99–1.09)
Lee and Weiss [17]	0.12 (8.9×10^{-3})	1.12 (0.93–1.35)
Johannes et al. [18]	−0.03 (1.2×10^{-2})	0.97 (0.78–1.20)
de Vries et al. [19]	0.07 (7.2×10^{-3})	1.07 (0.91–1.26)

*Daily dose of ICS, BDP or equivalent.
CI, confidence interval; ICS, inhaled corticosteroids.

Table 4. Pooled odds ratios and I^2 statistic relating risk of non-vertebral fracture to ICS use per 1000 µg*

Fixed effects OR (95% CI)	I^2 statistic (95% CI)	Random effects OR (95% CI)
1.08 (1.03–1.12)	78.8 (49.3–91.1)	1.12 (1.00–1.26)

*Daily dose of ICS, BDP or equivalent.
CI, confidence interval; ICS, inhaled corticosteroids; OR, odds ratio.

might account for this variation through meta-regression. Although a funnel plot and formal test of publication bias suggested this was not present, these tests are not likely to be reliable with only five studies analysed. A forest plot of the estimates of the slope coefficients is shown in Fig. 2. A plot of the log odds ratios together with the 95% CI for each individual study and the fitted random-effects risk is shown in Fig. 3. The magnitude of the risk, measured on the odds ratio scale, with ICS use was smaller than that associated with other commonly recognized risk factors (Table 5).

Discussion

This systematic review and meta-analysis showed an association between the dose of ICS and the risk of non-vertebral fracture, with the relative risk increasing by 12% for each 1000 µg per day of BDP or equivalent. The magnitude of this risk was considerably less than that reported for other common risk factors for fracture in the older adult.

Methodological issues

There were a number of methodological issues considered in the design of the meta-analysis that are relevant to the interpretation of the findings. Firstly, due to the rarity of non-vertebral fractures in the general population, even in older adults, there were no randomized placebo-controlled trials identified within the systematic review time frame. A large randomized-controlled trial, the 'TORCH' trial, a factorial design comparison of salmeterol and

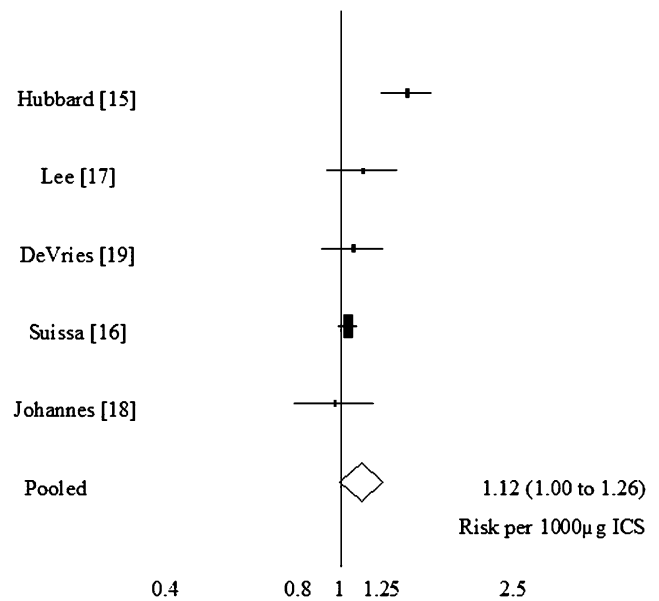


Fig. 2. Forest plot of the risk of non-vertebral fracture per 1000 µg increase in dose of inhaled corticosteroids (ICS) (beclomethasone dipropionate or equivalent), area of box proportional to precision of estimate.

1000 µg daily dose of inhaled fluticasone vs. placebo, was published in February 2007 [27]. This trial was not a dose-response trial and fracture was not a primary outcome variable; however, it is possible to estimate the hazard ratio for the outcome of any fracture in this trial for the dose of fluticasone used, equivalent to 2000 µg of BDP per day [28]. The actual count of fractures is not given in the published results but from the proportions of participants with fractures described, it is possible to calculate that 181/3098 participants randomized to arms with fluticasone and 158/3086 participants randomized to arms without fluticasone suffered a fracture. Using the approximate method of Pocock [29], this gives an estimated hazard ratio of 1.15 and an approximate P -value of 0.091 for the risk of fracture. As fracture in this trial was still a relatively rare outcome, the study only had a 40% power to detect a relative increase in fracture hazard of 1.2, from a placebo rate of 5%, with a mean follow-up of 3 years, to 6% in the fluticasone arms. Thus, the fracture outcome in the 'TORCH' trial was concordant with our estimate from case-control studies examined in this meta-analysis.

Two cohort studies were found by our systematic review. These studies could not be included in the meta-analysis as it would not have been possible to derive a slope coefficient for the dose-response relationship that could be pooled across studies. In addition, it was not appropriate to combine hazards ratios based on survival analysis with relative risks based on odds ratios, and the variance estimates were not comparable. The study by Van Staa et al. [25] found a hazard ratio of fracture for users of ICS compared with non-users of 1.11 for low dose (daily

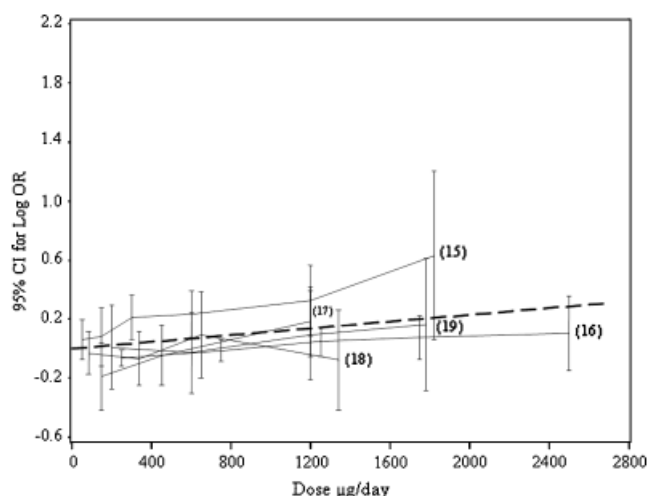


Fig. 3. Plot of log odds ratios [95% confidence interval (CI)] for risk of non-vertebral fracture by dose for individual studies (references shown in brackets) plus fitted risk (---).

dose < 300 µg daily BDP equivalent) and 1.28 for high dose (> 700 µg daily BDP equivalent). The study by Hubbard et al. [26] found a hazard ratio, adjusted for potential confounders such as age, sex and use of oral corticosteroids, of 4.21, for fracture in users of above 600 µg BDP equivalent a day compared with non-users. Thus, whereas the Van Staa et al. study [25] was consistent with our findings, the association for the highest dose in the study by Hubbard et al. [26] was considerably larger.

Although the total number of subjects included in our analysis exceeded 300 000 with over 128 000 (43%) using ICS, our use of case-control studies meant that the association we detected was susceptible to bias due to confounding of fracture risk with factors other than ICS use. The potential confounding factors include age, sex, concomitant routine or intermittent use of oral corticosteroids for disease control, the effect of immobility due to respiratory impairment, the different indications for ICS use such as asthma and COPD, variable levels of calcium intake, different vitamin D levels due to different sunlight exposure, other diseases associated with osteoporosis, other medication use including anti-osteoporosis medication and the different ICS prescribed. All the studies were matched on age and sex and adjusted for the use of oral corticosteroids, although they were variable in the other potential confounding variables used to calculate the adjusted risk estimates. It seems likely that this wide variation in the adjustment for confounding variables contributed to the identified heterogeneity in individual study estimates. The Suissa et al. study [16], which strongly influenced the pooled estimate of risk, by contributing most of the subjects and with the lowest variance of the studies, also adjusted for the widest range of potential confounding variables. It is possible that users of higher doses of ICS may have an increased fracture risk

Table 5. Relative risk of fracture with recognized factors in order of magnitude*

Study	Relative risk
One or more falls	4.7
Antipsychotic medication	2.8
Underweight [†]	2.4
Opioid analgesics	1.9
Cerebrovascular disease	1.9
Hypnotic medication	1.7
Current smoker	1.5
Inhaled corticosteroid use [‡]	1.1

*Derived from Hubbard et al. [26].

[†]BMI < 18.5 kg/cm².

[‡]ICS use: 1000 µg BDP or equivalent.

BDP, beclomethasone dipropionate; ICS, inhaled corticosteroids.

due to underlying disease severity, as suggested by de Vries et al. [19], who reported similar fracture rates among users of different asthma drugs. This potential effect will have been mitigated to some extent by our use of the adjusted estimates, in which there had been adjustment for confounding by disease severity through use of other severity markers. Another contributing factor may be the average age of the participants. The Johannes et al. study [18], which had a negative point estimate for the association between ICS dose and fracture risk, involved a substantially younger group than the other four studies, with 90% of subjects aged under 65 years, a group that is at a much lower risk of fracture than older subjects.

Another factor that might have contributed to the variability of the pooled estimate was the method of calculating the ICS dose. The time over which the daily dose average was calculated varied from study to study with a range of 1–4 years. If fracture risk is related to cumulative ICS exposure, then the extent to which the calculated average daily use over the individual study time frames reflects this cumulative risk may vary according to the length of time it is averaged over. Another factor that may affect the cumulative dose of ICS is compliance. This has not been taken into account by any of the studies in this meta-analysis; however, there is considerable evidence that compliance with inhaled medications, especially in the case of asthma, is poor [30]. As such, the amount of ICS that participants were actually exposed to may have been significantly lower than estimated, which would in turn influence any dose-response relationship.

With a relatively small number of studies included, we were unable to identify or use study-level co-variables to explore the heterogeneity in more detail, leading to our use of random-effects estimate. This means our pooled estimate has wider CIs than might have been the case if we had been able to determine groups of studies that were more homogenous.

Another difficulty with our estimate is that two of the case-control studies used the same database, the UKGPRD, from around the same time period [15, 19] (as did one of the cohort studies that was not included in the analysis [25]). Thus, these estimates may not be independent estimates of risk leading to our CIs being too narrow.

All studies included in the analysis reported the dose-response relationship for non-vertebral fractures. These variably included hip, hip or upper extremity or non-vertebral fractures depending on the study. While the effects of steroids may differ between the different sites of non-vertebral fracture, this could not be assessed in our study by conducting a formal meta-regression by fracture type, due to the small number of studies. If such a difference does exist, it could have contributed to the marked heterogeneity observed between studies. Most of the studies in our analysis [16–19] had point estimates for fracture risk at the lower doses that suggested less risk of fracture compared with non-use of ICS, although for all these studies the CIs for these estimates were also consistent with an increased risk. An advantage of our approach of fitting a single degree of freedom test for the dose-response relationship is our increased statistical power to detect a dose-response relationship, particularly as the relationship was not strong.

Our choice of non-vertebral fracture as an inclusion criterion was based on evidence that most non-vertebral fractures are recorded in GP records, in contrast to vertebral fractures that are uncommonly diagnosed clinically [4], with only a minority recorded in medical records. This requirement meant that the findings may not be directly relevant to the risk of vertebral fractures. However, we feel that this estimate of risk is clinically relevant as hip fracture is the most important fracture in terms of morbidity and risk of mortality and utilization of health resources [31].

Clinical significance

The clinical significance of these findings depends on the baseline risk of osteoporotic fracture. For example, the annual incidence of hip fracture in New Zealand is 3.2 per 1000 for men and 5.7 per 1000 for women aged over 65 years [32]. In this population, the use of 1000 µg of BDP or equivalent would increase the incidence of hip fracture from 3.2 to 3.4 and from 5.7 to 6.1 per 1000 per year, respectively. However, the absolute risk would increase more substantially in a population at greater baseline risk, such as those with a history of falls, in which 1000 µg BDP or equivalent would increase the incidence from 15 to 17 and 27 to 30 per 1000 per year, respectively. Although this high-risk population predominantly comprised older patients who received ICS treatment for COPD, these findings are still clinically important in relation to the predominantly younger population being treated with

ICS for asthma. Not only the current dose of ICS but also the cumulative total dose of ICS is likely to be associated with a higher non-vertebral fracture rate. As a result, ICS dose along with other modifiable risk factors for fractures should be considered not only in COPD patients but also in the asthma population, to attempt to decrease the risk of fracture in later life.

It is also possible to assess the clinical relevance of these findings by considering the relative risk of fracture with other risk factors. This comparison was made with data on risk associated with other recognized factors presented in the Hubbard *et al.* study [15] that was based on the UKGPRD and included in this meta-analysis. From this comparison, it was evident that high-dose ICS therapy has a considerably smaller relative risk than other common co-morbidities or medication use (Table 5).

Comparison with the dose-response relationship of other systemic effects

It is informative to compare the findings with the dose-response relationships that have been determined for other major systemic effects of adrenal suppression and cataracts. In a recent meta-analysis, we have reported that in adults with asthma the risk of adrenal suppression increases by about 1.18 for each 500 µg dose of BDP or equivalent [11]. The dose-response relationship of ICS and cataracts has also been defined recently in the large UKGPRD case-control study [33]. After adjustment for systemic steroids and consultation rate, the relative risk of cataract was 1.18 for the dose range 800–1600 µg per day and 1.69 for the high-dose range of adult patients taking >1600 µg per day of BDP or equivalent.

Comparison with the dose-response relationship of clinical efficacy

These findings contrast with the dose-response relationship for clinical efficacy in asthma, in which most of the therapeutic efficacy is obtained at doses around 400–500 µg of BDP or equivalent, with the mean dose achieving the maximum benefit being around 1000 µg per day [34–36]. This dose-response relationship applies to a wide range of outcomes from a reduction in airway inflammation to reducing symptoms and rescue β-agonist use, improvement in lung function and a reduction in the frequency and severity of exacerbations, as well as the risk of mortality [37]. However, there is considerable individual variability in response to ICS in asthma and it has been shown recently that smokers have relative resistance to the benefits of ICS therapy [38–40]. These observations provide support for the use of higher doses of between 1000 and 2000 µg of BDP or equivalent in patients with severe disease not controlled on lower doses or those who are smokers.

Conclusion

The main finding from this meta-analysis was of an association between fracture risk and increasing doses of ICS, with the relative risk of non-vertebral fracture increasing by about 12% for each 1000 µg increase in the daily dose of BDP or equivalent. This association, should it be causal, may be clinically relevant to patients at a high baseline risk of fracture, such as the very old with multiple risk factors and a history of previous osteoporotic fracture. However, the risk is considerably less than that due to other common co-morbidities and medication use.

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