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LOW-DOSE INHALED AND NASAL CORTICOSTEROID USE AND THE RISK OF CATARACTS

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ABSTRACT

Orally inhaled corticosteroid (ICS) use has been convincingly linked to an increase in the risk of cataracts although the risk at lower doses in common use remains uncertain. The potential risk of cataracts with the use of nasal corticosteroids (NCS) is unknown.

We performed a matched nested case-control analysis in a population based cohort of elderly people who had been dispensed medications for airway disease as identified through a universal drug benefit plan.

ICS use was associated with a dose related increase in both the risks of all cataracts and the risk of severe cataracts requiring extraction (RR 1.24 95%CI 1.18-1.31 per 1000 mcg per day of beclomethasone or the equivalent) and the increase in risk of severe cataracts was apparent even at daily doses of 500 mcg or less (RR 1.14 95%CI 1.08-1.20). An excess risk with NCS was not apparent for severe cataracts (RR 1.03 95%CI 0.99-1.07 per 100 mcg).

We conclude that, among the elderly, even low doses of ICS are associated with a small but significant excess risk of cataracts requiring extraction. Such an excess risk was not observed with NCS.

Abstract word count: 185

Key words: inhaled corticosteroids, nasal corticosteroids, cataracts, elderly, asthma, COPD.

INTRODUCTION

Cataracts are a major public health problem affecting almost 50% of adults over the age of 65 years and cataract extraction is the most common surgical procedure carried out in the U.S.[1] Furthermore, it has been estimated that by delaying the development of cataract formation by 10 years, 45% of these extractions would be avoided.[2] The use of orally inhaled corticosteroids (ICS) has been convincingly linked to an increase in the risk of cataracts in several epidemiologic studies.[3-5]

Cumming and colleagues[3] undertook screening of a general population for cataracts and demonstrated a clear association between the use of ICS and cataracts. The validity of this association was bolstered by the finding of a dose related increase in risk for posterior subcapsular cataracts, a particularly debilitating type of cataract.[1] Of particular concern was a more than two-fold increase in risk at daily doses of between 200 mcg and 400 mcg per day of beclomethasone, doses recommended for the large population with mild persistent asthma.[6] The doses of ICS were based on patient report, however, thus raising doubts as to the actual doses patients used. Garbe and co-workers found an increase in the risk of all cataracts combined which was particularly evident at daily doses of beclomethasone greater than 1000mcg, while the risk associated with lower doses was uncertain.[4] In a large general practice research database in the U.K., Jick and colleagues found a dose related increase in the risk of cataracts in subjects aged 40 years or more.[5] The risk appeared to be increased even at a prescribed dose of ICS of less than 500mcg per day of beclomethasone. Limitations of this study include the exclusion of subjects who had been prescribed oral or nasal

corticosteroids, thus limiting the ability to generalise the results to a significant proportion of patients with airway disease; the derivation of doses from prescriptions rather than from drugs dispensed, thus adding uncertainty about the actual doses consumed. Therefore the doses associated with an increase in risk can be questioned. None of these studies examined the independent risk of cataracts associated with the use of nasal corticosteroids (NCS). Furthermore, in all three studies, beclomethasone was responsible for the preponderance of exposure to inhaled corticosteroids with few if any patients receiving fluticasone, now a commonly prescribed medication in North America, and a medication for which concerns regarding a greater potential for systemic effects have been raised.[7;8]

We undertook to examine the association between the risk of cataracts among elderly subjects and the dispensing of low doses of ICS, as well as the risk associated with use of NCS, using a large population wide claims database.

METHODS

Source of data

We used the health databases of the Régie de l'assurance maladie du Québec (RAMQ), the agency responsible for administering the universal health insurance program of the province of Québec, Canada. The databases contain information on demographics, all medical services rendered, along with the diagnostic code of the service (ICD-9 code), and, for people aged 65 years or older, all out-patient prescription medications dispensed. Information obtained from the Quebec prescription claims

databases has been previously validated.[9]

Study design

A population-based cohort design with a nested case-control analysis was used. The source population consisted of all subjects who, between January 1, 1988 and December 31, 2001, were 65 years of age or older and were dispensed at least one of the following respiratory medications during this period: any form of ß-agonist, theophylline, ipratropium bromide, sodium cromoglycate, nedocromil, ketotifen, leukotriene antagonists, or inhaled corticosteroids. A cohort was formed from this source population by identifying all subjects with three or more prescriptions for these medications in any one-year period and on at least two different dates. Cohort entry was taken as the date of the third prescription. In order to assure a minimum of 4 years of information on use of medications and to limit the study, as far as possible, to incident cases of cataract, we limited the current study to subjects with at least 4 years of follow-up and without a diagnosis of cataract or a cataract extraction during this initial 4 year period.

Cases of cataracts were the cohort members with a first diagnosis of cataract (ICD-9 code 366) or a procedure code for cataract extraction during follow-up. We also defined the subset of cases with severe cataracts, defined as a cataract requiring an extraction within 2 years from a first diagnosis.

For each case, 4 controls were selected randomly from among subjects who entered the cohort on the same month and year as the case and who were born within six months of the birth date of the case. For the cases for whom controls could not be

found, matching was widened to the year of cohort entry rather than month and year. Controls also had to be at risk on the date of the outcome event in the corresponding case (the index date); that is they could not have been identified as having a cataract, moved from the Province, or died, as of this date. This date was taken as the index date for the controls.

Corticosteroid exposure

All prescriptions of corticosteroid medications dispensed during the four years prior to the index date were obtained for all cases and controls and classified according to their formulation, dose, quantity, duration, and date of dispensing. These include, in inhaled and nasal forms, beclomethasone, budesonide, triamcinolone, fluticasone and flunisolide, and, in oral form, hydrocortisone, cortisone, prednisone, prednisolone, triamcinolone, methylprednisolone, betamethasone and dexamethasone.

To combine the different corticosteroids, dose equivalencies were established. For oral corticosteroids, the dose equivalencies were taken directly from Goodman and Gilman.[10] Equivalent doses are prednisone 5 mg, prednisolone 5 mg, hydrocortisone 20 mg, cortisone 25 mg, triamcinolone 4 mg, methylprednisolone 4mg, betamethasone 0.75 mg and dexamethasone 0.75 mg. The estimation of equivalencies for ICS and NCS were chosen on the basis of relative topical potency and what experts consider to be comparable low doses according to the NAEP expert panel II report, figures 3-5b and 3-5c[11] and the Canadian asthma consensus statement summary, Table 8.[12] Accordingly, the equivalent doses for inhaled and nasal corticosteroids are beclomethasone 100Φg,

budesonide 80Φg, triamcinolone 200Φg, fluticasone 50Φg and flunisolide 200Φg.

Covariates

Covariates included, gender, hospitalization in the previous 4 years, the severity of respiratory disease, as well as other conditions or medications associated with the risk of cataracts.[1] We quantified the severity of respiratory disease, independently of inhaled corticosteroid use, by counting the number of dispensed prescriptions of ß-agonists, ipratropium bromide and theophylline. We assessed the concurrent use of oral corticosteroids as the cumulative prednisone equivalent dose dispensed during the 4-year period prior to the index date.

Co-morbid disease was identified by the dispensing of disease specific medications. Diabetes was identified by prescriptions for insulin and oral hypoglycaemic drugs. Cardiovascular drugs included cardiotropes and vasodilators. Hypertension was identified by the dispensing of anti-hypertensives, not including diuretics. Since diuretics are used so extensively, these were considered as a distinct risk factor. Rheumatic drugs included gold salts, methotrexate, azathioprine, hydroxychloroquine and chloroquine. Adjustment was also carried out for the use of medications which have been specifically associated with the risk of cataract such as topical corticosteroids, allopurinol and major tranquilizers.[1;13] For adjustment purposes, exposure to these drugs was considered as present or not, based on whether or not they had been dispensed at any time during the prior 4-year period.

Statistical analysis

All analyses were based on techniques for matched data. The primary analysis was based on the corticosteroid exposure during the four-year period prior to the index date with non-use during the 4-year period as the reference. We used conditional logistic regression to calculate crude and adjusted odds ratios for inhaled and nasal corticosteroid use in relation to the occurrence of cataracts and severe cataracts. In a nested case control study such as ours, the odds ratios correctly estimate the incidence rate ratios. [14] A cumulative dose during the 4-year span was computed by summing separately the dose equivalents of all prescriptions of the inhaled and nasal formulations. The mean daily dose was taken as the cumulative dose divided by the time from the date of the first prescription to the index date.

Age and calendar time were inherently accounted for by the matching. Further adjustment factors included gender, prior hospitalization, severity of respiratory disease, as well as all other covariates measuring conditions associated with the risk of cataract. Since oral corticosteroid use is clearly associated with an increased risk of cataract,[1] we carried out separate analyses among subjects with and without exposure to oral corticosteroids in the prior 4 years. When examining the risk associated with ICS, adjustment was carried out for use of NCS and vice versa. All analyses were carried out using SAS statistical software (SAS Institute Inc. Carey, NC).

RESULTS

The cohort comprised 101,805 subjects, including 27,708 cases with a first

diagnosis of cataract or a cataract extraction, of which 10,754 were considered severe. Characteristics of cases and controls are provided in Table I. Information is provided for all cases and their respective controls as well as for the more severe cases which resulted in surgical extraction within two years of the diagnosis. The subjects were elderly with a mean age of almost 78 years. Cases tended to have more co-morbid disease, although the differences were small. Cases had been dispensed more ophthalmic corticosteroids and eye drops than their respective controls. Cumulative exposure to oral corticosteroids over the prior 4 years had been significantly greater among cases.

Table 1: Characteristics of cases and controls

	Cases (n = 27708)	Controls (n = 110832)	Severe cases* (n = 10754)	Controls (n = 43016)
Age (mean ± std)	**77.8 ± 5.21**	**77.8 ± 5.21**	**77.7 ± 5.06**	**77.7 ± 5.06**
Female sex (%)	**54.0**	**48.3**	**52.8**	**47.9**
Hospitalized in last 4 years (%)	**70.4**	**65.5**	**69.8**	**65.4**
Drug treated conditions during the four years prior to index date:				
Cardiovascular disease (%)	**59.7**	**56.4**	**59.3**	**56.4**
Diabetes (%)	**14.6**	**13.0**	**14.5**	**12.9**
Hypertension (%)	**41.0**	**39.1**	**41.1**	**39.0**
Rheumatic disease (%)	**1.5**	**1.1**	**1.5**	**1.2**
Use of medications possibly associated with cataract risk during the four years prior to index date				
Allopurinol (%)	**5.8**	**5.3**	**6.0**	**5.2**
Injectable corticosteroids (%)	**8.9**	**7.6**	**8.9**	**7.8**

Ophthalmic corticosteroids (%)	**11.2**	**7.5**	**10.7**	**7.5**
Dermatologic corticosteroids(%)	**48.7**	**45.4**	**46.6**	**45.1**
Diuretics (%)	**52.8**	**49.8**	**52.0**	**49.7**
Gold Salts (%)	**0.2**	**0.2**	**0.2**	**0.2**
Myotics (%)	**4.4**	**2.8**	**5.5**	**2.7**
NSAID (%)	**76.0**	**73.2**	**75.1**	**73.0**
Major tranquilizers (%)	**5.9**	**6.7**	**5.2**	**6.8**
Use of oral corticosteroids in the 4 years prior index date				
Any use (%)	**11.5**	**9.5**	**40.3**	**33.3**
Cumulative dose ** **in all subjects in mg (mean ± std)**	**904.7 ± 2543.1**	**611.8 ± 1974.9**	**1082.8 ± 2859.6**	**642.4 ± 2037.9**
Cumulative dose ** **in users in mg (mean ± std)**	**2383.6 ± 3676.1**	**1878.2 ± 3097.7**	**2689.3 ± 3998.9**	**1927.9 ± 3160.0**

*** Cases of cataract which required extraction within 2 years of the diagnosis.**

**** Cumulative dose computed in prednisone equivalent units**

In Table II relative risks of any cataract appear to be increased for both inhaled and nasal corticosteroids after adjustment for co-morbidity, each other and exposure to oral corticosteroids. For ICS, the risk is increased significantly even at daily doses less than 500 mcg per day in beclomethasone equivalent units (RR 1.11; 95% CI 1.07-1.14) and rises to a maximum increase of 44 % (RR 1.44; 95%CI 1.31-1.57) at doses between 1500 mcg and 2000 mcg per day. Overall the risk of any cataract with the use of ICS increases by 19% (RR 1.19; 95%CI 1.15-1.23) per additional 1000 mcg of beclomethasone or the equivalent per day. For NCS, there is also an apparent increase in risk even at doses below 100 mcg per day (RR 1.16; 95%CI 1.12-1.21), although, in

contrast to the orally inhaled route, the dose response is less obvious.

Table II: Crude and adjusted rate ratios of any cataract for the mean daily dose of inhaled and nasal corticosteroids during the four-year period prior to the index date

		Cases	Controls	Crude RR	Adjusted*	
					RR	95% CI
Number of subjects		**27708**	**110832**			
Inhaled Corticosteroids (ICS)						
Dose used during four years prior to index date						
Mean daily dose in mcg (mean ± std)		**342.1±476.1**	**299.0±448.5**	**1.24**	**1.19****	**1.15 - 1.23**
Mean daily dose (mcg) range	**Mean daily dose (mcg)*****					
None	**0**	**10176**	**45662**	**1.0**	**1.0**	**Reference**
>0 to 500 mcg	**196**	**10199**	**39600**	**1.17**	**1.11**	**1.07 - 1.14**
>500 to 1000 mcg	**734**	**4341**	**15855**	**1.26**	**1.18**	**1.13 - 1.35**
>1000 to 1500 mcg	**1205**	**1987**	**6668**	**1.38**	**1.27**	**1.20 - 1.40**
>1500 to 2000 mcg	**1701**	**788**	**2370**	**1.55**	**1.44**	**1.31 - 1.57**
>2000 mcg	**2458**	**217**	**677**	**1.50**	**1.36**	**1.16 - 1.59**
Nasal Corticosteroids (NCS)						
Dose used during four years prior to index date						
Mean daily dose in mcg (mean ± std)		**17.3 ± 57.2**	**14.1 ± 51.2**	**1.11**	**1.08****	**1.05 - 1.10**
Mean daily dose (mcg) range	**Mean daily dose (mcg)*****					
None	**0**	**21556**	**90265**	**1.0**	**1.0**	**Reference**
>0 to 100 mcg	**34**	**4649**	**15714**	**1.24**	**1.16**	**1.12 - 1.21**
>100 to 200 mcg	**141**	**893**	**2861**	**1.31**	**1.21**	**1.12 - 1.31**

>200 mcg	**316**	**610**	**1992**	**1.28**	**1.18**	**1.07 - 1.30**

*** Adjusted for all the factors in Table 1 as well as for the cumulative dose of the other class of topical corticosteroids.**

**** Rate ratio per additional 1000 mcg (beclomethasone-equivalent units) of mean daily dose of inhaled corticosteroids or 100 mcg of nasal corticosteroids.**

***** Mean daily dose (in mcg of beclomethasone-equivalent units) estimated by the cumulative dose divided by the treatment period, among the controls in that category**

The dose response analyses were repeated for the more severe cases of cataracts which required surgical extraction in the two years following diagnosis (Table III). The increases in risk seen with ICS are quite similar to those observed for all cataracts; there is a 24% increase in risk of a severe cataract (RR 1.24; 95%CI 1.18-1.31) per 1000 mcg per day of beclomethasone or the equivalent and the increase in risk is apparent even at daily doses of 500 mcg or less (RR 1.14 95%CI 1.08-1.20). For NCS, however, there was no significant increase in the risk of severe cataracts.

Table III: Crude and adjusted rate ratios of severe cataracts for the mean daily dose of inhaled and nasal corticosteroids during the four-year period prior to the index date

		Cases	Controls	Crude RR	Adjusted*	
					RR	95% CI
Number of subjects		**10754**	**43016**			
Inhaled Corticosteroids (ICS)						
Dose used during four years prior to index date						
Mean daily dose in mcg (mean ± std)		**372.7±493.9**	**305.6±453.0**	**1.38**	**1.24****	**1.18 - 1.31**
Mean daily dose (mcg) range	**Mean daily dose (mcg)*****					
None	**0**	**3716**	**17454**	**1.0**	**1.0**	**Reference**
>0 to 500 mcg	**196**	**3908**	**15374**	**1.22**	**1.14**	**1.08 - 1.20**

>500 to 1000 mcg	**737**	**1813**	**6316**	**1.40**	**1.26**	**1.17 - 1.35**
>1000 to 1500 mcg	**1206**	**869**	**2673**	**1.60**	**1.37**	**1.25 - 1.51**
>1500 to 2000 mcg	**1701**	**355**	**932**	**1.89**	**1.59**	**1.39 - 1.83**
>2000 mcg	**2489**	**93**	**267**	**1.74**	**1.40**	**1.09 - 1.79**
Nasal Corticosteroids (NCS)						
Dose used during four years prior to index date						
Mean daily dose in mcg (mean ± std)		**16.3 ± 57.4**	**14.2 ± 51.3**	**1.08**	**1.03****	**0.99 - 1.07**
Mean daily dose (mcg) range	**Mean daily dose (mcg)*****					
None	**0**	**8570**	**35008**	**1.0**	**1.0**	**Reference**
>0 to 100 mcg	**34**	**1632**	**6117**	**1.09**	**1.03**	**0.97 - 1.09**
>100 to 200 mcg	**142**	**312**	**1111**	**1.15**	**1.04**	**0.92 - 1.19**
>200 mcg	**317**	**240**	**780**	**1.26**	**1.12**	**0.96 - 1.30**

*** Adjusted for all the factors in Table 1 as well as for the cumulative dose of the other class of topical corticosteroids.**

**** Rate ratio per additional 1000 mcg (beclomethasone-equivalent units) of mean daily dose of inhaled corticosteroids or 100 mcg of nasal corticosteroids.**

***** Mean daily dose (in mcg of beclomethasone-equivalent units) estimated by the cumulative dose divided by the treatment period, among the controls in that category**

Fluticasone accounted for 14.9% of the prescriptions of ICS among the controls. There was no difference in the risk of severe cataracts for users of fluticasone (RR 1.12 95%CI 1.04-1.19) as compared to users of any ICS (RR 1.19 95%CI 1.13-1.25).

Table IV provides an analysis of the risk of any cataract for various doses of ICS, among subjects who have, or who have not, been dispensed oral corticosteroids in the prior four years. While the dose response appears somewhat steeper among subjects also dispensed oral corticosteroids, the risk of any cataract remains elevated even

among subjects without such exposure. Among subjects without concomitant exposure to oral corticosteroids, there is a 12 % increase in the risk of any cataract (RR 1.12 95%CI 1.07-1.18) for every 1000 mcg of beclomethasone or the equivalent per day. The association is of similar magnitude when considering only severe cataracts as shown in Table V.

Table IV: Rate ratios of any cataract for the mean daily dose of orally inhaled corticosteroids dispensed during

the four-year period prior to the index date, stratified by use of oral corticosteroids (CS).

	Cases	Controls	Crude RR	Adjusted*	
				RR	95% CI
Among subjects with no oral CS use during the 4 years prior to index date					
Number of subjects	**17191**	**74733**			
Mean daily dose in mcg (mean ± std)	**184 ± 347**	**174 ± 347**	**1.11**	**1.12****	**1.07 - 1.18**
Mean daily dose (mcg)* range**					
None	**8968**	**41278**	**1.0**	**1.0**	**Reference**
>0 to 500 mcg	**5988**	**24193**	**1.16**	**1.13**	**1.09 - 1.17**
>500 to 1000 mcg	**1467**	**6198**	**1.12**	**1.13**	**1.06 - 1.20**
>1000 to 1500 mcg	**530**	**2100**	**1.20**	**1.21**	**1.09 - 1.33**
>1500 mcg t0 2000 mcg	**207**	**772**	**1.27**	**1.28**	**1.09 - 1.50**
>2000 mcg	**31**	**192**	**0.77**	**0.78**	**0.53 - 1.14**
Among subjects with oral CS use during the 4 years prior to index date					
Number of subjects	**10517**	**36099**			
Mean daily dose in mcg (mean ± std)	**600 ± 541**	**557 ± 520**	**1.19**	**1.20****	**1.15 - 1.26**
Mean daily dose (mcg)* range**					
None	**1208**	**4384**	**1.0**	**1.0**	**Reference**
>0 to 500 mcg	**4211**	**15407**	**1.01**	**1.03**	**0.96 - 1.11**
>500 to 1000 mcg	**2874**	**9657**	**1.11**	**1.15**	**1.07 - 1.25**
>1000 to 1500 mcg	**1457**	**4568**	**1.20**	**1.23**	**1.12 - 1.35**
>1500 to 2000 mcg	**581**	**1598**	**1.38**	**1.43**	**1.27 - 1.61**
>2000 mcg	**186**	**485**	**1.47**	**1.48**	**1.23 - 1.79**

* Adjusted for all the factors in Table 1 as well as for the cumulative dose of nasal corticosteroids.

** Rate ratio per additional 1000 mcg (beclomethasone-equivalent units) of mean daily dose of inhaled corticosteroids

*** Mean daily dose (in mcg of beclomethasone-equivalent units) estimated by the cumulative dose divided by the treatment period, among the controls in that category

Table V: Rate ratios of severe cataracts for the mean daily dose of orally inhaled corticosteroids used during the four-year period prior to index date, stratified by use of oral corticosteroids (CS).

	Cases	Controls	Crude RR	Adjusted*	
				RR	95% CI
Among subjects with no oral CS use during the 4 years prior to index date					
Number of subjects	6424	28682			
Mean daily dose in mcg (mean ± std)	195 ± 355	178 ± 348	1.18	1.16**	1.07 - 1.25
Mean daily dose (mcg)*** range					
None	3261	15692	1.0	1.0	Reference
>0 to 500 mcg	2254	9322	1.19	1.15	1.08 - 1.22
>500 to 1000 mcg	609	2479	1.23	1.20	1.09 - 1.32
>1000 to 1500 mcg	209	831	1.27	1.23	1.05 - 1.45
>1500 mcg	81	287	1.42	1.33	1.03 - 1.72
>2000 mcg	10	71	0.71	0.66	0.34 - 1.29
Among subjects with oral CS use during the 4 years prior to index date					
Number of subjects	4330	14334			
Mean daily dose in mcg (mean ± std)	636 ± 550	562 ± 525	1.33	1.27**	1.18 - 1.36
Mean daily dose (mcg)***range					
None	455	1762	1.0	1.0	Reference
>0 to 500 mcg	1654	6052	1.08	1.1	0.97 - 1.24
>500 to 1000 mcg	1204	3837	1.27	1.25	1.10 - 1.42

>1000 to 1500 mcg	**660**	**1842**	**1.46**	**1.39**	**1.20 - 1.6**
>1500 to 2000 mcg	**274**	**645**	**1.77**	**1.66**	**1.38 - 2.00**
>2000 mcg	**83**	**196**	**1.78**	**1.60**	**1.20 - 2.13**

*** Adjusted for all the factors in Table 1 as well as for the cumulative dose of nasal corticosteroids.**

**** Rate ratio per additional 1000 mcg (beclomethasone-equivalent units) of mean daily dose of inhaled corticosteroids**

***** Mean daily dose (in mcg of beclomethasone-equivalent units) estimated by the cumulative dose divided by the treatment period, among the controls in that category**

DISCUSSION

We have shown an increase in the risk of cataracts including severe cataracts requiring surgical extraction, in association with the dispensing of ICS among elderly patients. While the excess risk was small, it increased significantly with increasing dose and was present even at 500 mcg or less per day of beclomethasone or the equivalent dose of other inhaled corticosteroids. There was no evidence of an excess risk associated with the orally inhaled form of fluticasone as compared to other orally inhaled corticosteroids, mainly beclomethasone and budesonide. The relationship between the risk of cataracts and use of NCS was less apparent. The dose response was less obvious than with ICS when examining the risk of all cataracts, and no increase in risk of cataracts requiring extraction was seen in association with dispensing of NCS.

For ICS, our results are consistent with those of Cumming[3] and of Jick[5] who also found an increase in the risk of cataracts even with low daily doses of ICS. The strengths of the current study are several. All subjects in the population over the age of 65years with more than occasional use of respiratory medications were included. Only first cataracts occurring after a 4 year period of observation were included so as to avoid

masking a relationship to corticosteroid medications which might have resulted if a cataract had been detected previously and treatment modified as a consequence. Exposure to corticosteroids was as dispensed rather than prescribed medication, thus increasing the likelihood that patients actually took these medications. Due to the large number of subjects and the frequency of exposure, we were able to adjust for the concomitant use of other topical and systemic steroid use so as to isolate the independent effect of ICS.

Our study also has several limitations. Firstly, our results are only applicable to elderly subjects. Secondly, we did not obtain clinical records to confirm the diagnosis of cataract. The analysis restricted to cases who undergo extraction within two years assures that these cataracts are real and of clinical consequence, however. The use of corticosteroids has been most closely linked to occurrence of posterior subcapsular cataracts.[1;3] We were unable to distinguish between the different types of cataract and likely included cataracts not influenced by use of corticosteroids. This will decrease the strength of the relationship observed such that we have likely underestimated the increase in risk of posterior subcapsular cataracts with use of ICS. While we were able to measure and control for the effects of important confounders such as diabetes and other conditions and medications potentially associated with the risk of cataracts, we had no information on other potential confounding factors such as smoking and body mass index.[2] Controlling for diabetes and hypertension likely partially accounts for the effect of obesity. Furthermore, since, through reduced physical activity, obesity may result from, rather than cause cataracts, adjustment for body mass index may not be appropriate.

The lack of information on smoking may be more problematical. Partial reassurance is provided by the study of Jick and colleagues who found that adjustment for smoking did not alter the association between ICS and risk of cataracts.[5]

We examined exposure to ICS and NCS over the four year period prior to the diagnosis of a first cataract. We cannot be certain that the effects observed might not be due to use of oral corticosteroids or the use of higher doses of topical corticosteroids prior to this four year period. Our adjustment for the severity of respiratory disease as reflected by the intensity of respiratory medication use, other than corticosteroids, may partially control for use of corticosteroids in the more distant past. Our results, however, mirror clinical reality in that remote use of medications by patients is often unknown or inaccurate and it is current doses of medication that are of concern and can be modified.

Our results have important implications for the treatment of asthma and COPD in the elderly. For asthma, an important effort needs to be made to reduce the dose of ICS as much as possible, for example, by the use of ICS in combination with long-acting bronchodilators or anti-leukotrienes.[15;16] Given the limited efficacy of ICS in COPD,[17;18] the balance of evidence in favour of their use is less obvious.

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