

USE OF INHALED CORTICOSTEROIDS AND THE RISK OF CATARACTS

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ABSTRACT

Background The use of systemic corticosteroids is a risk factor for the development of posterior subcapsular cataracts, but the association between inhaled corticosteroids and cataracts is uncertain.

Methods We conducted a population-based, cross-sectional study of vision and common eye diseases in an urban area of the Blue Mountains, near Sydney, Australia. We recruited 3654 people 49 to 97 years of age; the participation rate was 82 percent. We collected information by questionnaire on potential risk factors for cataracts, including the current or prior use of inhaled corticosteroids (beclomethasone or budesonide). Photographs of the subjects' lenses were graded, without information on the subjects, to determine the presence and severity of cortical, nuclear, and posterior subcapsular cataracts.

Results Three hundred seventy subjects reported using inhaled corticosteroids, 164 currently and 206 previously. Among these subjects, after adjustment for age and sex, there was a higher prevalence of nuclear cataracts (relative prevalence, 1.5; 95 percent confidence interval, 1.2 to 1.9) and posterior subcapsular cataracts (relative prevalence, 1.9; 95 percent confidence interval, 1.3 to 2.8) than among the subjects with no inhaled-corticosteroid use, but the prevalence of cortical cataracts was not significantly higher (relative prevalence, 1.1; 95 percent confidence interval, 0.9 to 1.3). Higher cumulative lifetime doses of beclomethasone were associated with higher risks of posterior subcapsular cataracts (P for trend <0.001); the highest prevalence (27 percent) was found in subjects whose lifetime dose was over 2000 mg (relative prevalence, 5.5). Adjusting for the use of systemic corticosteroids and other potential confounders had little effect on the magnitude of the associations. The associations with posterior subcapsular cataracts, but not those with nuclear cataracts, were less marked when the analyses were restricted to subjects who had never used systemic corticosteroids.

Conclusions The use of inhaled corticosteroids is associated with the development of posterior subcapsular and nuclear cataracts. (*N Engl J Med* 1997; 337:8-14.)

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CATARACTS are classified according to their anatomical location; the most common types are cortical, nuclear, and posterior subcapsular. Posterior subcapsular cataracts are the most visually disabling type and account for the majority of cataract extractions. With advancing age, cortical and nuclear cataracts become increasingly important causes of visual loss.¹

The use of systemic corticosteroids is an estab-

lished risk factor for the development of posterior subcapsular cataracts.^{2,3} A case report in 1980 suggested that inhaled corticosteroids may also cause cataracts,⁴ but most subsequent studies of patients attending asthma clinics have found no such association.⁵⁻¹⁰ Because nearly all subjects in studies to date have also used systemic corticosteroids, it is difficult to differentiate the effects of inhaled corticosteroids from those of systemic corticosteroids. Furthermore, most studies have involved only children, in whom cataracts are extremely rare. We report the results of a community-based study of cataracts in older adults, including a substantial number of users of inhaled corticosteroids who never used systemic corticosteroids.

METHODS

The Blue Mountains Eye Study is a population-based study of vision and common eye diseases in an urban population in the Blue Mountains region, west of Sydney, Australia. The details of the recruitment methods have been reported elsewhere.¹¹ In brief, after conducting a door-to-door census of the region, we invited all permanent residents born before January 1, 1943, to visit a local clinic for a detailed eye examination. Of the 4433 people identified as eligible by the census, 3654 visited the study clinic between January 1992 and January 1994.

Ethical approval for the study was obtained from the Human Research Ethics Committee of the Western Sydney Area Health Service, and written informed consent was obtained from all the study subjects.

Eye Examinations and Grading of Cataracts

The lens of each eye was photographed after dilation of the pupil with 1 percent tropicamide and 10 percent phenylephrine. The protocol for lens photography and grading closely followed the Wisconsin Cataract Grading System and is described in detail elsewhere.¹²⁻¹⁴ To assess the severity of nuclear cataracts, slit-lamp photographs were taken (SL-7E, Topcon Optical, Tokyo, Japan). Retroillumination photographs of the anterior and posterior lens were taken to assess the presence and severity of cortical and posterior subcapsular cataracts (Cataract CT-R camera, Neitz Instruments, Tokyo).

The severity of nuclear cataracts was assessed on a five-point scale by comparing the photographs of the subjects' eyes with a set of four standard photographs. A grade 1 cataract was defined as less dense than, or as dense as, the cataract on the first standard photograph. A grade 2 cataract was more dense than the cataract on the first photograph, but no more dense than the cataract on the second photograph. Cataracts of grades 3, 4, and 5 were similarly defined.

Cortical cataracts were identified and their severity graded by placing a circular grid over the Neitz photographs that was divided into eight wedges of equal size and a central circle. The graders

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estimated the proportion of each of these nine areas that was involved by cataract. The percentages were summed to give an estimate of the total area of the lens that was affected by the cataract.

Posterior subcapsular cataracts were graded similarly. Photographs in which either the vertical or the horizontal diameter of the pupils was less than 4 mm were excluded from the analyses of cortical cataracts. The standard photographs of nuclear cataracts and the grid were provided by Dr. Barbara Klein of the University of Wisconsin, Madison. All the photographs were assessed by one of two graders who were unaware of any data on the patients. The quadratic weighted kappas for the reproducibility of measurements between graders were 0.79 for nuclear cataracts (measured in 260 eyes), 0.78 for cortical cataracts (in 379 eyes), and 0.57 for posterior subcapsular cataracts (in 383 eyes).¹⁵

Data on the presence or absence of cortical and posterior subcapsular cataracts were missing for about 3 percent of subjects, either because the photographs could not be graded or none were taken. Mainly because of camera malfunction (a short circuit in the camera wiring that caused the photographs to be underexposed), 1045 subjects (29 percent) did not have photographs suitable for nuclear-ataract grading. These subjects were similar to the subjects with photographs that could be graded. The mean ages of the two groups were similar (66.1 years for the subjects without photographs as compared with 65.7 years for the subjects with photographs), as were the proportions with cortical cataracts (25 percent vs. 23 percent), posterior subcapsular cataracts (6 percent vs. 7 percent), a history of using inhaled corticosteroids (12 percent vs. 10 percent), and a history of using systemic corticosteroids (10 percent vs. 8 percent).

Questionnaire Data

A questionnaire on a wide range of possible risk factors for cataracts was administered by an interviewer. The subjects also brought all their current medications to the study center, where the names of the medications were recorded. They were asked how long they had used each one and whether they had ever taken any other medications for more than three months. A series of questions was specifically concerned with corticosteroid use, including these: "Have you ever used a beclomethasone inhaler, a brown-colored inhaler used to treat asthma and other chest conditions?" and "Have you ever taken corticosteroid tablets, such as prednisone, cortisone, or dexamethasone, for asthma, arthritis, or another condition?" Further questions concerned the usual number of puffs of beclomethasone per day or week and the total duration of use of systemic corticosteroids. Data on the duration of use were missing for 40 of 164 current users of inhaled corticosteroids. Among those who had used beclomethasone at any time, data on the number of puffs per week were missing for 97 of 339 subjects; data on the duration of use of systemic corticosteroids were missing for 51 of 303 subjects.

The questionnaire data were used to classify the subjects as having ever (either currently or in the past) or never used inhaled corticosteroids (beclomethasone, budesonide, or both). The subjects who had used beclomethasone were further classified according to the usual number of puffs per week (14 or less, 15 to 28, or more than 28). For current users, the data on the number of years of beclomethasone use and the usual number of puffs per week were combined to give an estimated lifetime dose (less than 1000 mg, 1000 to 1999 mg, or 2000 mg or more). (We assumed that each puff contained 100 μ g of beclomethasone.) Unfortunately, the duration of use was unknown in the case of past users. Current and past users of systemic corticosteroids were classified according to the total number of years those drugs had been used (less than 1, 1 to 4.9, or 5 or more).

The questionnaire also asked about known risk factors for cataracts, including the subject's history of smoking, diabetes, and hypertension. Subjects were asked if a doctor had ever told them that they had diabetes or high blood pressure. Systolic and diastolic blood pressure was measured. Hypertension was defined as a history of high blood pressure reported by the subject, a diastolic

blood pressure over 95 mm Hg, a systolic blood pressure over 160 mm Hg, or a combination of these. Our measure of socioeconomic status was the attainment of a further degree or certificate after high school. We assessed sun-related skin damage by examining the arms, hands, and face and rated it on a four-level scale (none, mild, moderate, and severe).

Statistical Analysis

All the analyses involved only data on the subject's more severely affected eye. Initially, age- and sex-adjusted relative-prevalence ratios were calculated in stratified analyses¹⁶ with the data on each type of cataract dichotomized (for nuclear cataracts, below grade 4 vs. grade 4 or higher; for cortical cataracts, less than 5 percent involvement of the lens vs. 5 percent or more; and for posterior subcapsular cataracts, no lens involvement vs. any involvement). Further analysis was performed by ordinal regression, with the cumulative odds model,¹⁷ which gives odds ratios for the probability of having a cataract of a particular severity (or worse) as compared with the probability of having a less severe cataract or none. Nuclear cataracts were modeled as a four-level variable (with grades 4 and 5 combined), and posterior subcapsular cataracts were included as a variable with three levels (no lens involvement, less than 5 percent involvement, or 5 percent involvement or greater). Relative-prevalence ratios cannot be calculated from ordinal regression models. Because nuclear cataracts are common, the reported odds ratios are larger than the relative-prevalence ratios.

In ordinal regression models, we tested for trends among categorized ordered variables by selecting the median value in each category and then modeling exposure as a single continuous variable. Mantel's extension of the Mantel-Haenszel test was used to test for trend in stratified analyses.¹⁶

All the analyses were done with SAS statistical software (SAS, Cary, N.C.). P values of less than 0.05 were considered to indicate statistical significance. All P values were based on two-sided tests.

RESULTS

There were 3654 subjects in the Blue Mountains Eye Study; the rate of participation was 82 percent. The subjects ranged in age from 49 to 97 years (median, 65). One hundred eight subjects were aphakic, had intraocular lenses in both eyes, or both. Among those for whom at least one lens photograph could be evaluated for the specific type of cataract, 217 (6 percent of 3444 subjects) had posterior subcapsular cataracts in some degree, 817 (24 percent of 3435) had more than 5 percent of a lens involved by a cortical cataract, and 467 (19 percent of 2501) had grade 4 or 5 nuclear cataracts.

Data on corticosteroid use were available for 3313 subjects. Of these, 111 had used both systemic and inhaled corticosteroids, 241 had only used inhaled corticosteroids, and 177 had only used systemic corticosteroids. (For 33 subjects there were data on the use of oral corticosteroids [15 subjects] or inhaled corticosteroids [18 subjects], but not both.) Of the 164 current users of inhaled corticosteroids, 103 used beclomethasone and 66 used budesonide (5 subjects used both). Because budesonide became available in Australia only in late 1991, beclomethasone was the only inhaled corticosteroid that the subjects could have used for more than a year or two.

Table 1 shows the distribution of the risk factors for cataracts according to the subjects' history of corticosteroid use. There were no important differences

TABLE 1. CHARACTERISTICS OF 3313 STUDY SUBJECTS ACCORDING TO THEIR HISTORY OF CORTICOSTEROID USE.*

| CHARACTERISTIC | TYPE OF CORTICOSTEROID USED | | | |
|--|-----------------------------|------------------------------|-------------------------------|--------------------------------------|
| | NONE (N = 2784) | INHALED ONLY (N = 241) | SYSTEMIC ONLY (N = 177) | INHALED AND SYSTEMIC (N = 111) |
| Mean age — yr | 66.1 | 66.1 | 66.8 | 63.4 |
| Female sex — no. of subjects (%) | 1563 (56) | 131 (54) | 113 (64) | 76 (69) |
| Education beyond high school — no. of subjects (%) | 1132 (42) | 96 (41) | 67 (39) | 50 (46) |
| History of smoking — no. of subjects (%) | | | | |
| Never smoked | 1353 (49) | 96 (40) | 81 (46) | 47 (44) |
| Former smoker | 1012 (37) | 108 (45) | 62 (36) | 48 (44) |
| Current smoker | 391 (14) | 37 (15) | 31 (18) | 13 (12) |
| Medical conditions — no. of subjects (%)† | | | | |
| Diabetes | 159 (6) | 21 (9) | 14 (8) | 5 (5) |
| Hypertension | 1394 (50) | 121 (51) | 93 (53) | 51 (46) |
| Sun-related skin damage — no. of subjects (%) | | | | |
| None | 2030 (74) | 187 (78) | 128 (73) | 88 (80) |
| Moderate | 581 (21) | 39 (16) | 34 (19) | 18 (16) |
| Severe | 134 (5) | 14 (6) | 13 (7) | 4 (4) |

*Data on corticosteroid use were missing for 341 of the 3654 study subjects. For the remaining 3313 subjects, data were missing for the following variables: education (112 subjects), history of smoking (34), diabetes (19), hypertension (28), and skin damage (43). In calculating percentages for each characteristic, the number of subjects for whom there were complete data for that characteristic was used as the denominator.

†Diabetes was reported by the subjects themselves. Hypertension was defined as a systolic blood pressure over 160 mm Hg, a diastolic blood pressure over 95 mm Hg, a history of high blood pressure reported by the subject, or a combination of these.

between users and nonusers of corticosteroids or between users of inhaled corticosteroids and users of systemic corticosteroids.

Table 2 shows age- and sex-adjusted relative-prevalence ratios for the associations between the use of inhaled and systemic corticosteroids and the presence of cataracts. The use of inhaled corticosteroids at any time was associated with a significantly increased prevalence of nuclear cataracts (relative prevalence, 1.5; 95 percent confidence interval, 1.2 to 1.9) and posterior subcapsular cataracts (relative prevalence, 1.9; 95 percent confidence interval, 1.3 to 2.8). An increased prevalence of posterior subcapsular cataracts was associated with current use of inhaled corticosteroids (relative prevalence, 2.6; 95 percent confidence interval, 1.7 to 4.0) but not with past use. Higher cumulative lifetime doses of beclomethasone were associated with higher risks of posterior subcapsular cataracts. The highest prevalence (27 percent) of posterior subcapsular cataracts was among subjects whose lifetime dose of beclomethasone was over 2000 mg (relative prevalence, 5.5; 95 percent confidence interval, 2.3 to 13.0). This group also had a high prevalence (40 percent) of grade 4 or 5 nuclear cataracts (relative prevalence, 4.0; 95 percent confidence interval, 1.8 to 9.3). Current use of inhaled corticosteroids was associated with an increased prevalence of cortical cataracts

(relative prevalence, 1.4; 95 percent confidence interval, 1.1 to 1.7).

The use of systemic corticosteroids was associated with an increased prevalence of posterior subcapsular cataracts; there was a dose-response relation between the duration of use and the prevalence of such cataracts. The only significant association between the use of systemic corticosteroids and the presence of nuclear or cortical cataracts was a relative prevalence of 1.6 (95 percent confidence interval, 1.0 to 2.4) for cortical cataracts among subjects who had used systemic corticosteroids for more than five years.

Ordinal regression (with posterior subcapsular cataracts graded in three levels and nuclear cataracts graded in four levels) was used to assess the associations of cataracts with inhaled corticosteroids, with adjustment for potential confounding according to age, sex, smoking history, diabetes, hypertension, sun-related skin damage, and use of systemic corticosteroids. Further control for confounding by the use of systemic corticosteroids was achieved by excluding subjects who had ever used systemic corticosteroids from the analyses.

Adjustment for multiple confounders in models that included users of systemic corticosteroids had little effect on the strength of the association between the use of inhaled corticosteroids and the

TABLE 2. ADJUSTED RELATIVE-PREVALENCE RATIOS AND 95 PERCENT CONFIDENCE INTERVALS FOR THE ASSOCIATIONS BETWEEN THE USE OF CORTICOSTEROIDS, INHALED OR SYSTEMIC, AND THE PRESENCE OF CATARACTS.*

| VARIABLE | No. OF SUBJECTS | TYPE OF CATARACT | | |
|--|-----------------|--|---------------|-----------------------|
| | | CORTICAL | NUCLEAR | POSTERIOR SUBCAPSULAR |
| | | prevalence ratio (95 percent confidence interval) | | |
| Inhaled corticosteroids | | | | |
| Never used | 3011 | 1.0 | 1.0 | 1.0 |
| Used at some time | 370 | 1.1 (0.9–1.3) | 1.5 (1.2–1.9) | 1.9 (1.3–2.8) |
| Formerly | 206 | 0.9 (0.7–1.2) | 1.6 (1.1–2.3) | 1.1 (0.6–2.0) |
| Currently | 164 | 1.4 (1.1–1.7) | 1.5 (1.1–2.0) | 2.6 (1.7–4.0) |
| Beclomethasone (puffs/wk) | | | | |
| Weekly dose among all users | | | | |
| ≤14 puffs | 96 | 0.9 (0.6–1.4) | 1.4 (0.9–2.4) | 1.3 (0.6–2.8) |
| 15–28 puffs | 87 | 1.3 (0.9–1.8) | 0.9 (0.5–1.7) | 2.1 (1.1–3.9) |
| >28 puffs | 59 | 1.4 (0.9–2.1) | 1.9 (1.1–3.2) | 3.1 (1.7–5.7) |
| P for trend | | 0.06 | 0.05 | <0.001 |
| Lifetime inhaled dose among current users† | | | | |
| <1000 mg | 40 | 0.9 (0.5–1.6) | 0.5 (0.2–1.4) | 2.5 (1.1–5.8) |
| 1000–1999 mg | 15 | 1.0 (0.3–3.5) | 1.3 (0.2–8.0) | 5.4 (2.0–14.7) |
| ≥2000 mg | 15 | 1.7 (0.8–3.6) | 4.0 (1.8–9.3) | 5.5 (2.3–13.0) |
| P for trend | | 0.39 | 0.08 | <0.001 |
| Systemic corticosteroids | | | | |
| Never used | 3114 | 1.0 | 1.0 | 1.0 |
| Used at some time | 303 | 1.1 (0.9–1.3) | 1.2 (0.9–1.6) | 1.5 (1.0–2.3) |
| Formerly | 244 | 1.1 (0.8–1.3) | 1.1 (0.8–1.6) | 1.5 (0.9–2.4) |
| Currently | 59 | 1.2 (0.8–1.7) | 1.3 (0.8–2.2) | 1.7 (0.8–3.6) |
| Duration of use among all users | | | | |
| <1 yr | 175 | 1.2 (0.9–1.5) | 1.2 (0.8–1.8) | 1.1 (0.6–2.1) |
| 1–4.9 yr | 44 | 0.6 (0.3–1.1) | 0.9 (0.4–2.4) | 1.8 (0.7–4.7) |
| ≥5 yr | 33 | 1.6 (1.0–2.4) | 1.6 (0.9–2.8) | 2.7 (1.3–5.6) |
| P for trend | | 0.22 | 0.14 | 0.009 |

*Data are adjusted for age and sex by the Mantel-Haenszel method. Information was incomplete for the following variables: use of inhaled corticosteroids (data were missing for 273 subjects), use of systemic corticosteroids (237 subjects), weekly dose of beclomethasone (97 of 339 subjects who used beclomethasone at any time), lifetime inhaled dose of beclomethasone (33 of 103 current users), and duration of systemic corticosteroid use (51 of 303 subjects who used systemic corticosteroids at any time).

†Data on this variable were obtainable only for current users and were calculated as follows: number of years of beclomethasone use × 52, × the usual number of puffs per week, × 0.1 (the number of milligrams delivered per puff).

presence of posterior subcapsular cataracts (Table 3). However, in the model restricted to subjects who had never used systemic corticosteroids, the dose-response relation between the lifetime dose of beclomethasone and the presence of a posterior subcapsular cataract was less evident (P = 0.06).

Adjusted data on the association between inhaled corticosteroids and nuclear cataracts are shown in Table 4. High doses of beclomethasone were associated with nuclear cataracts in both the models that included systemic-corticosteroid users and those that did not.

Because people may alter their use of medications once a cataract has been diagnosed, we repeated all the analyses in the 3028 subjects who said that they had never been told they had a cataract. The results

for these subjects were essentially the same as those for all study subjects (data not shown).

DISCUSSION

Our community-based study of older Australians suggests that the use of inhaled corticosteroids is associated with an increased risk of posterior subcapsular cataracts and nuclear cataracts. This is consistent with the relation between the use of systemic corticosteroids and the presence of posterior subcapsular cataracts.² It has been increasingly recognized that inhaled corticosteroids have systemic effects. They can suppress the hypothalamic-pituitary-adrenal axis, and they may cause osteoporosis.^{9,18,19} Our finding that the use of inhaled corticosteroids is more strongly associated with posterior

TABLE 3. ADJUSTED ODDS RATIOS AND 95 PERCENT CONFIDENCE INTERVALS DERIVED FROM ORDINAL REGRESSION MODELS FOR THE ASSOCIATION BETWEEN THE USE OF INHALED CORTICOSTEROIDS AND THE PRESENCE OF POSTERIOR SUBCAPSULAR CATARACTS.

| VARIABLE | INHALED CORTICOSTEROIDS | | LIFETIME DOSE OF BECLOMETHASONE (mg)† | | | P FOR TREND |
|---|-------------------------|-----------------|---------------------------------------|----------------|-----------------|-------------|
| | NEVER USED | CURRENTLY USED* | <1000 | 1000–1999 | ≥2000 | |
| odds ratio (95 percent confidence interval) | | | | | | |
| All subjects | | | | | | |
| Model adjusted for age and sex | 1.0 | 3.5 (2.1–5.8) | 3.5 (1.3–9.3) | 6.3 (1.7–23.4) | 13.2 (4.2–41.5) | <0.001 |
| Multivariate model‡ | 1.0 | 3.0 (1.7–5.1) | 2.6 (0.9–7.4) | 5.1 (1.3–19.8) | 10.0 (3.0–33.2) | <0.001 |
| No. of cases | 141 | 20 | 5 | 3 | 4 | |
| No. of subjects | 2616 | 137 | 34 | 15 | 13 | |
| Subjects who never used systemic corticosteroids | | | | | | |
| Model adjusted for age and sex | 1.0 | 3.2 (1.7–6.0) | 2.6 (0.6–11.3) | 3.6 (0.4–33.8) | 4.6 (0.6–35.5) | 0.05 |
| Multivariate model‡ | 1.0 | 3.2 (1.7–6.1) | 2.7 (0.6–11.7) | 4.2 (0.4–39.6) | 3.8 (0.5–29.8) | 0.06 |
| No. of cases | 133 | 12 | 2 | 1 | 1 | |
| No. of subjects | 2492 | 82 | 19 | 6 | 6 | |

*This group was limited to subjects using beclomethasone, budesonide, or both at the time of the study.

†Data on lifetime inhaled doses were obtainable only for current users of beclomethasone and were calculated as described in the second note to Table 2.

‡Data in the multivariate model were adjusted for age, sex, education, history of smoking, diabetes (as reported by the subjects), hypertension (as defined in the second note to Table 1), sun-related skin damage, and years of use of systemic corticosteroids (in the model involving all subjects). Because of missing data on cataracts, corticosteroid use, or covariates, 695 subjects were excluded from the multivariate models involving all subjects and 624 subjects were excluded from the models involving subjects who had never used systemic corticosteroids.

TABLE 4. ADJUSTED ODDS RATIOS AND 95 PERCENT CONFIDENCE INTERVALS DERIVED FROM ORDINAL REGRESSION MODELS FOR THE ASSOCIATION BETWEEN THE USE OF INHALED CORTICOSTEROIDS AND THE PRESENCE OF NUCLEAR CATARACTS.

| VARIABLE | INHALED CORTICOSTEROIDS | | LIFETIME DOSE OF BECLOMETHASONE (mg)† | | | P FOR TREND |
|---|-------------------------|-----------------|---------------------------------------|---------------|----------------|-------------|
| | NEVER USED | CURRENTLY USED* | <1000 | 1000–1999 | ≥2000 | |
| odds ratio (95 percent confidence interval) | | | | | | |
| All subjects | | | | | | |
| Model adjusted for age and sex | 1.0 | 1.7 (1.2–2.5) | 1.0 (0.5–2.0) | 1.1 (0.3–3.9) | 5.5 (1.6–19.2) | 0.02 |
| Multivariate model‡ | 1.0 | 1.7 (1.1–2.5) | 1.0 (0.5–2.0) | 1.0 (0.3–3.7) | 5.4 (1.5–9.1) | 0.02 |
| No. of cases | 321 | 24 | 3 | 1 | 4 | |
| No. of subjects | 1886 | 107 | 31 | 10 | 9 | |
| Subjects who never used systemic corticosteroids | | | | | | |
| Model adjusted for age and sex | 1.0 | 2.0 (1.2–3.2) | 1.0 (0.4–2.5) | 0.8 (0.1–4.3) | 8.9 (1.5–51.9) | 0.03 |
| Multivariate model‡ | 1.0 | 1.8 (1.1–3.0) | 1.0 (0.4–2.5) | 0.7 (0.1–4.0) | 9.0 (1.5–52.3) | 0.04 |
| No. of cases | 302 | 20 | 1 | 1 | 3 | |
| No. of subjects | 1804 | 66 | 17 | 5 | 5 | |

*This group was limited to subjects using beclomethasone, budesonide, or both at the time of the study.

†Data on lifetime inhaled doses were obtainable only for current users of beclomethasone and were calculated as described in the second note to Table 2.

‡Data in the multivariate model were adjusted for age, sex, education, history of smoking, diabetes (as reported by the subjects), hypertension (as defined in the second note to Table 1), sun-related skin damage, and years of use of systemic corticosteroids (in the model involving all subjects). Because of missing data on cataracts, corticosteroid use, or covariates, 1455 subjects were excluded from the multivariate models involving all subjects and 1328 subjects were excluded from the models involving subjects who had never used systemic corticosteroids.

subcapsular cataracts than with other types of cataracts is not surprising, because this region of the lens is particularly sensitive to metabolic insult, including those caused by diabetes and oral corticosteroids.^{2,20} The biologic mechanisms by which corticosteroids cause posterior subcapsular cataracts remain uncertain but are likely to include the inhibition of sodium-potassium pumps in the lens epithelium, leading to the accumulation of water in lens fibers and the agglutination of lens proteins.^{20,21} A previous study of inhaled corticosteroids and cataracts in older adults involved 48 people (mean age, 61 years) attending a specialist asthma clinic.⁸ All but one had used oral corticosteroids at some time. Slit-lamp examination revealed that 14 subjects had posterior subcapsular cataracts. That study found no association between the use of inhaled corticosteroids and the presence of the cataracts.

Because cataracts in children are very rare, even quite large increases in risk may be missed in studies of young people. Simons and colleagues performed slit-lamp examinations of the lenses of 96 young patients with asthma who had used inhaled corticosteroids for an average of five years, and none had any evidence of cataract.⁵ Tinkelman et al. found no cataracts in 108 children treated with inhaled beclomethasone for one year.⁷ Abuekteish et al. examined 140 young people with asthma who used inhaled corticosteroids and found a 13-year-old girl who had received numerous courses of oral corticosteroids.⁶ Nassif et al. identified one posterior subcapsular cataract among 32 children treated with inhaled corticosteroids for an average of 1.3 years; all the subjects had used oral corticosteroids in the past.⁹

The strengths of our study include the high participation rate, the careful grading of the lens photographs to identify the presence and severity of cataracts, the large sample, and the control for confounding variables. Because the study was community-based, we were able to compare the prevalence of cataracts between users and nonusers of inhaled corticosteroids, and we could also examine the associations in a large subgroup of subjects who had never used systemic corticosteroids.

Our study had several limitations. The amount of information we collected on corticosteroid use was more limited than that in previous clinic-based studies. For example, perhaps the best measure of exposure to inhaled corticosteroids, the cumulative lifetime dose of beclomethasone, could only be estimated in current users. Another limitation is the large amount of missing data regarding both exposure-related variables and confounders. For example, the multivariate-adjusted model for the association between the lifetime dose of beclomethasone and the presence of posterior subcapsular cataracts included only 78 percent of the study subjects. Finally,

our study was cross-sectional; the temporal relation between the use of inhaled corticosteroids and the presence of cataracts is difficult to assess.

Our study was conducted in 1992 and 1993. Inhaled budesonide was approved for use in Australia in late 1991. Hence, beclomethasone was the only inhaled corticosteroid used for any extended period. We have no reason to suspect, however, that the effect of budesonide would differ from that of beclomethasone.

Several criteria are commonly used to assess whether a statistically significant association in an epidemiologic study represents a true causal relation.¹⁶ The association we found between inhaled corticosteroids and posterior subcapsular cataracts fulfills several of these criteria. The association was strong, with posterior subcapsular cataracts three times more prevalent in users of inhaled corticosteroids than in nonusers. There was a strong dose-response relation. The relation is biologically plausible. Two other criteria were not adequately fulfilled: consistency and temporality. Our findings need to be replicated in different groups, and prospective studies should examine whether the use of inhaled corticosteroids precedes the onset of cataract.

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