

Letter to the Editor

Risk of cataracts in the Childhood Asthma Management Program Cohort

To the Editor:

Use of systemic corticosteroids is a well-established risk factor for the development of posterior subcapsular cataracts (PSCs) in both children and adults.¹ Dose and duration of inhaled corticosteroids (ICSs) have been reported to be independent risk factors for the development of PSCs in older patients.² The occurrence of PSCs is rare in children, and studies of children treated with ICSs have not found an increased risk of PSCs.³⁻⁵ We previously reported no risk of cataracts in 955 children in the Childhood Asthma Management Program (CAMP) assessed by means of lens photography after 4 to 6 years (mean, 4.3 years) of 400 µg/d budesonide administered by means of Turbuhaler, 16 mg/d nedocromil, or placebo. However, one child in the budesonide group was given a diagnosis of a barely measurable PSC on slit lamp examination 5 months after photography.⁵

The CAMP cohort has been followed continuously since closure of the trial in 1999. In 2005, 2 additional participants (both from the budesonide arm) reported PSCs, with 1 requiring surgery. In response to these reports and in consultation with the CAMP Data and Safety Monitoring Board, all CAMP participants were urged to obtain a dilated slit lamp examination specifically for the presence of cataracts (see [Appendices E1 and E2](#) in this article's Online Repository at www.jacionline.org). The findings from the resulting examinations plus the 3 reports of cataracts obtained previously form the basis of this report.

Three outcomes were defined for each participant: examination for cataract, any cataract finding, and any posterior finding. Covariates included cumulative doses of ICSs and oral corticosteroid for asthma to the date of the cataract examination. The ICSs included the blinded budesonide and unblinded ICSs prescribed during the trial and ICSs self-reported as taken for asthma during the observational posttrial follow-up. Prednisone bursts during the posttrial follow-up were assumed to conform to the CAMP trial regimen (up to 60 mg for each of 2 days followed by up to 30 mg for each of 2 days).

The association of each outcome with randomized treatment group and with ICS and oral corticosteroid use for asthma categorized as "ever" versus "never" was assessed by means of χ^2 analysis and logistic regression. Association of cataract posterior findings with the cumulative dose of ICS and cumulative dose of oral corticosteroid was assessed by means of logistic regression. Each cumulative dose was modeled first as a continuous variable and then as 3 indicator variables corresponding to tertiles of increasing dose. Lastly, each cumulative dose was modeled as a score based on the tertiles as a test for a dose-response effect. Analyses were performed with SAS 9.1 (SAS Institute, Inc, Cary, NC) or STATA 9.2 (StataCorp, College Station, Tex) software.

Two hundred thirty-two participants aged 15 to 26 years were examined, 22.3% of the original CAMP cohort ($n = 1,041$). Median duration from randomization to examination was 12 years (range, 4-14 years), and median duration from lens photography to examination was 8 years (range, 0.4-9 years). Median duration of ICS use among those using ICSs was 4.0 years (range, 0-13 years), and median 4-day dose (per burst) of

prednisone during CAMP for those ever taking prednisone for asthma during the CAMP study was 150 mg (range, 15-180 mg).

Sixteen participants were assessed as having cataract findings, of whom 12 were classified as having posterior findings (see [Table E1](#) in this article's Online Repository at www.jacionline.org). The percentage of participants obtaining examinations was similar across randomized treatment groups (22.8% budesonide, 22.1% nedocromil, and 22.0% placebo; $P = .96$; [Table I](#)). Among those examined, there was no evidence of increased cataracts in the budesonide group compared with the placebo group (odds ratio [OR], 1.6; 95% CI, 0.5-4.9; $P = .44$) or any evidence of increased posterior findings (OR, 1.3; 95% CI, 0.4-4.7; $P = .67$; [Table I](#)).

Participants ever using corticosteroids for asthma were more likely to obtain a cataract examination (25.8% ever using ICSs vs 12.8% never using ICSs, $P < .0001$, [Table I](#); 23.6% ever using oral corticosteroids vs 16.4% never using oral corticosteroids, $P = .03$, [Table I](#)). However, in those examined the risk of cataract findings did not differ by ICS use (OR, 0.8, ever vs never; 95% CI, 0.2-2.9; $P = .71$) or by oral corticosteroid use (OR, 1.1, ever vs never; 95% CI, 0.2-5.2; $P = .88$; [Table I](#)). Similar results were obtained for the risk of posterior finding. There was no association of cataract or posterior findings with cumulative ICS dose or cumulative oral corticosteroid dose ([Table II](#)).

Our findings suggest that long-term administration of ICSs in the recommended low to medium doses is not a significant risk factor for the development of PSCs in children, adolescents, and young adults. We did not find an association of cataracts or specifically PSCs with ICS use. These findings are consistent with the initial CAMP report based on evaluation of lens photographs of 92% of the participants after 4 to 6 years of treatment.⁵ This now becomes the longest study to date for the development of cataracts in children treated with ICSs, and our findings are consistent with those of 3 other nonrandomized studies of long-term ICS therapy in children.^{3,4,6}

Chronic systemic corticosteroids are associated with a risk of PSCs in children, as well as adults. Reports in the literature vary widely but indicate that 15% to 35% of children receiving daily oral corticosteroids for at least 1 year have PSCs.^{7,8} Risk factors for the development of PSCs include daily dose (>10 mg/d), duration (>2 years), and method of administration (daily vs every other day). It is possible that some children with multiple courses of oral prednisone per year had PSCs that then regressed, as has been previously reported.⁹

We report a 5.2% prevalence of posterior findings in our participants, which is much higher than the 0.2% in healthy young adults quoted from population-based studies.^{1,2} However, these studies used reports of clinically significant cataracts. In that regard our finding of 1 patient requiring surgery for cataracts is not significantly different from that reported in the National Health and Nutrition Examination Survey 2007-2008 vision questionnaire database for participants 14 to 25 years old (1/232 vs 2/1,621; $P = .33$, Fisher exact test).¹⁰ Our high prevalence could be a consequence of our specific request that the eye care provider look for cataracts. Additionally, the finding of more cataracts on slit lamp examination than on lens photography was recently reported.¹¹

A weakness of our report is that only 22.3% of the CAMP population obtained a dilated slit lamp examination; our power to

TABLE I. Examination for cataracts and cataract findings by randomized treatment and ever versus never use of corticosteroids for asthma

	Examined			Cataract findings* in those examined					Posterior findings† in those examined				
No.	No.	Percentage	No.	Percentage	OR‡	95% CI	P value§	No.	Percentage	OR‡	95% CI	P value§	
A. Randomized treatment group													
Budesonide	311	71	22.8	7	9.9	1.6	0.5-4.9	.44	5	7.0	1.3	0.4-4.7	.67
Nedocromil	312	69	22.1	3	4.4	0.7	0.2-2.7	.56	3	2.9	0.5	0.1-2.8	.44
Placebo	418	92	22.0	6	6.5				5	5.4			
Total	1,041	232	22.3	16	6.9				12	5.2			
P value		.96		.43					.54				
B. Use of inhaled corticosteroid in CAMP trial or observational study													
Ever	760	196	25.8	13	6.6	0.8	0.2-2.9	.71	9	4.6	0.5	0.1-2.1	.36
Never	281	36	12.8	3	8.3				3	8.3			
Total	1,041	232	22.3	16	6.9				12	5.2			
P value		<.0001		.71					.35				
C. Use of oral corticosteroid in CAMP trial or observational study													
Ever	846	200	23.6	14	7.0	1.1	0.2-5.2	.88	10	5.0	0.8	0.2-3.8	.77
Never	195	32	16.4	2	6.3				2	6.3			
Total	1,041	232	22.3	16	6.9				12	5.2			
P value		.03		.88					.77				

*Cataract findings include, for example, dense PSC, mild PSC, radial cataract, congenital, nuclear cataract, cortical spokes, flecks, lamellar and posterior subcapsular haze, and sutural opacities.

†Posterior findings include PSC, posterior subcapsular opacity, hint of PSC, posterior opacity, very early posterior subcapsular change, posterior opacity, trace PSC, and posterior subcapsular haze on any examination.

‡OR: budesonide/nedocromil versus placebo (A) and ever versus never (B and C).

§Wald χ^2 test for OR different from 1.

|| χ^2 Test for difference in proportion among treatment groups.

TABLE II. Cataracts and cataract findings by cumulative ICS dose and prednisone dose in 232 participants who obtained a dilated slit lamp examination*

	Cataract findings					Posterior findings				
	OR	95% CI	P value	P value†	P value‡	OR	95% CI	P value	P value†	P value‡
Continuous cumulative ICS and prednisone dose										
Male sex	0.73	0.3-2.1	.56			0.29	0.1-1.1	.08		
Age at randomization (per year)	1.12	0.9-1.4	.38			1.02	0.8-1.4	.86		
ICS (per mg)	1.00	1.0-1.0	.52			1.00	1.0-1.0	.82		
Prednisone (per mg)	1.00	1.0-1.0	.50			1.00	1.0-1.0	.40		
Tertiles of cumulative ICS and prednisone dose										
Male sex	0.74	0.3-2.2	.58			0.28	0.1-1.1	.07		
Age at rz (per year)	1.12	0.9-1.4	.40			1.02	0.8-1.4	.88		
ICS										
1-408 mg (vs none)	0.18	0.2-1.9	.15	.20	.79	0.17	0.2-1.8	.14	.46	.97
409-897 mg (vs none)	1.56	0.4-6.6	.55			0.83	0.2-4.1	.82		
≥898 mg (vs none)	0.71	0.1-3.8	.69			0.48	0.1-3.1	.44		
Prednisone										
1-465 mg (vs none)	1.33	0.2-7.7	.75	.95	.62	0.95	0.1-6.0	.96	.92	.57
466-1,440 mg (vs none)	1.30	0.2-8.2	.78			0.71	0.1-6.0	.75		
≥1441 mg (vs none)	1.69	0.3-10.8	.58			1.34	0.2-10.0	.77		

*Dose is cumulative through date of examination for cataracts.

†P value for all 3 categorical terms combined.

‡P value for linear trend across 3 categories.

detect a difference in risk is very low, as indicated by the broad 95% confidence limits on our risk estimates. Nevertheless, ours is one of the largest studies in children with asthma to date, and despite those who had greater corticosteroid exposure being more likely to have obtained an examination, we did not find any association between cataract findings and exposure to corticosteroids for asthma (Tables I and II). Another weakness was lack of standardization in the ophthalmic examination and the prompt to

eye care providers to look specifically for evidence of cataracts. However, this represents what happens in the real world outside of standardized clinical trials. Additionally, our dose data are a mix of prescribed dose (during the trial) and reported dose taken (during the follow-up phases). Finally, we did not include use of nasal and topical corticosteroids in the analysis or use of corticosteroids for conditions other than asthma. However, in a population-based case-control study, exposure to topical

corticosteroids did not affect the association between cataract and use of ICSs.²

Our findings of a lack of cumulative effect of ICSs and short bursts of oral corticosteroids does not rule out the possibility that high daily doses of ICSs will contribute to cataract formation, particularly in patients with other risk factors.³⁻⁵

In conclusion, the long-term use of ICSs in the recommended ranges in combination with occasional bursts of oral prednisone during childhood was not associated with an increased risk of cataracts. Thus regular monitoring for cataracts does not appear to be warranted in children, adolescents, and young adults with asthma being treated with low/medium-dose ICSs without other significant risk factors.

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*The members of the CAMP Research Group are shown in Appendix E3, which is available in this article's Online Repository at www.jacionline.org.

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the National Institutes of Health; is a committee chair for the American Academy of Pediatrics; and is on the Board of Directors for ASTHMA, Inc. H. W. Kelly is an ad hoc member of the advisory panels for GlaxoSmithKline, AstraZeneca, and MAP Pharmaceuticals and is on the speakers' bureau for AstraZeneca. The rest of the authors have declared that they have no conflict of interest.

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APPENDIX E1: LETTER AND CATARACT FACT SHEET PROVIDED TO EACH CAMP PARTICIPANT

Dear CAMPer/Parents of CAMPers,

We would like to thank you for your continued participation in the CAMPCS/2 study. With your help, we are still gathering and publishing important information about asthma that allows us to better understand how to most effectively treat children and young adults with asthma. This would not be possible without YOU!

As we have stressed throughout the study, your safety is of great importance to us. We promised to keep you informed about any potential safety or other issues that might arise over time.

What is the new information?

During the past 10 years of study of the more than 1,000 CAMPers, three CAMPers have developed cataracts in the lenses of their eyes. While cataracts are known to occur in children and young adults, the risk of developing a cataract is thought to be small. According to one source, in a study of 1000 children over 10 years, one would expect two children to develop cataracts, but another source suggests that less than one case of cataract would be expected in 1000 children studied 10 years.

How does this affect me now?

We want you to be aware of these findings. Although we don't know the cause of the three cataracts that have developed among CAMPers, to be cautious, we encourage you to have an eye exam to see if a cataract is present.

Is this the usual eye exam I receive when I need new glasses or contact lenses?

In addition to the visual acuity test (common eye chart test, which measures ability to see at various distances), the pupils of your eyes will need to be widened (dilation) with eye drops to allow close-up examination of the lens. This part of the eye exam will need to be done by an ophthalmologist or an optometrist. An optician (someone who prescribes glasses or contact lenses only) cannot perform this type of exam.

What do I tell the ophthalmologist or optometrist?

Tell the ophthalmologist or optometrist that you need a dilated slit lamp examination to check for presence of cataracts, particularly posterior subcapsular cataracts. We have prepared a letter which you may give to the ophthalmologist or optometrist.

What do I do if a cataract is found?

You should see an ophthalmologist if you have not already seen one, to discuss treatment for the cataract. Also, please contact the CAMP office and report this finding. CAMP cannot pay for follow-up or treatment of any cataract that is found, but we think it important to document any events that occur.

Should I change the way I use asthma medications now?

No, you should not. The benefits to asthma control from inhaled or oral corticosteroids are considerable. If you are found

to have a cataract, contact your asthma care provider to discuss what effect, if any, this would have on your use of asthma medications.

Will my health insurance pay for this exam?

This type of exam is covered by most insurance plans. Your primary care physician or the physician that primarily manages your asthma can refer you for the examination. It can also be done through most vision care centers. We can provide reimbursement of up to \$200.00 for your costs of the examination.

What if I don't have insurance or have trouble getting a referral?

If there are any difficulties, we can recommend whom to see for this exam. In addition, if there are problems with getting the exam covered by your insurance, we can provide reimbursement of up to \$200.00 for your costs of the examination.

How do I get reimbursed?

Obtain a receipt for any costs you pay for the examination. Send or bring these documents to the CAMPCS/2 office. The CAMPCS/2 staff will then process these documents for your reimbursement up to \$200.

Please see the attached sheet for more information on cataracts. If you have any additional questions or concerns, we would be happy to speak to you further and you can call us at the CAMP office.

Best regards,
CAMP PI and coordinator

APPENDIX E2: LETTER AND FORM FOR EYE CARE PROVIDER

Dear eye care provider,

The bearer of this letter is a participant in the Childhood Asthma Management Program, a clinical study funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, to evaluate and compare the long-term (10 year) effects on lung growth and development among three different asthma treatments given during the first 4 years of the study, including inhaled corticosteroids. The study is in its final year and has received three reports of suspected or definite posterior subcapsular cataracts among the 1041 participants, although there were confounding issues with all three reports (eg, use of oral and/or topical steroids). The CAMP study has reported the findings to the CAMP participants and is encouraging them to obtain a dilated slit lamp examination to check for presence of cataracts, particularly posterior subcapsular cataracts. We would appreciate your indicating your major findings below.

CAMP will provide the participant with a payment covering a portion of the costs of the examination. This completed form will be used by the participant to demonstrate that he/she has obtained the examination.

We appreciate your assistance in helping our CAMP participants.

Sincerely,

CAMP PI and clinic coordinator (name/contact info)	
Participant name: _____	Date of exam: _____
Ophthalmologist/optometrist name and contact info: _____	
Findings for right eye	Findings for the left eye
Visual acuity: _____	Visual acuity: _____
History of trauma to the eye?	History of trauma to the eye?
Yes/No	Yes /No
If yes, please describe:	If yes, please describe:
Are cataracts present? Yes /No	Are cataracts present? Yes /No
If yes, please describe findings:	If yes, please describe findings:

APPENDIX E3: MEMBERS OF THE CAMP RESEARCH GROUP

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Resource centers

Data Coordinating Center, the Johns Hopkins University, Baltimore, Md: James Tonascia, PhD (Director). Patricia Belt; Karen Collins; Betty Collison; Ryan Colvin, MPH; John Dodge; Michele Donithan, MHS; Cathleen Ewing; Rosetta Jackson; Hope Livingston; Jill Meinert; Girlie Reyes; Michael Smith; Alice L. Sternberg, ScM; Mark L. Van Natta, MHS; Annette Wagoner; Laura Wilson, ScM; Robert Wise, MD; Katherine Yates, ScM.

Project Office, National Heart, Lung, and Blood Institute, Bethesda, Md: Virginia Taggart, MPH (Project Officer); Lois Eggers; James Kiley, PhD; Howard Moore; Gang Zheng, PhD. Paul Albert, PhD (1991-1999); Suzanne Hurd, PhD (1991-1999); Sydney Parker, PhD (1991-1994); Pamela Randall (1992-2003); Margaret Wu, PhD (1991-2001).

Committees

Data and Safety Monitoring Board: Michelle Cloutier, MD (Chair); John Connett, PhD; Leona Cuttler, MD; Frank Gilliland, MD, PhD. Clarence E. Davis, PhD (1993-2003); Howard Eigen, MD (1993-2009, Chair); David Evans, PhD (1993-2007); Meyer Kattan, MD (1993-2007); Rogelio Menendez, MD (1993-2007); F. Estelle R. Simons, MD (1993-2007); Sanford Leikin, MD (1993-1999).

Steering Committee: Robert Strunk, MD (Study Chair); N. Franklin Adkinson, MD; Robert Annett, PhD (1992-1995, 1997-1999); Bruce Bender, PhD; Mary Caesar, MHS (1994-1996); Reuben Cherniack, MD (Study Chair 1993-2007); Thomas R. DuHamel, PhD (1992-1994, 1996-1999); Anne Fuhlbrigge, MD; Hartmut Grasmann, MD; H. William Kelly, PharmD; Henry Levison, MD (1992-1996); Alan Lincoln, PhD (1994-1995); Ian MacLusky, MD (1999-2006); Bennie McWilliams, MD (1992-1998); Curtis L. Meinert, PhD; Sydney Parker, PhD (1991-1994); Joe Reisman, MD, FRCP(C), MBA (1991-1999); Denise Rodgers; Kay Seligsohn, PhD (1996-1997); Gail G. Shapiro, MD (1991-2006); Marian Sharpe (1993-1994); D Sundström (1998-1999); Stanley Szeffler, MD; Virginia Taggart, MPH; Martha Tata, RN (1996-1998); James Tonascia, PhD; Scott Weiss, MD, MS; Barbara Wheeler, RN, BSN (1993-1994); Paul Williams, MD; Robert Wise, MD; Robert Zeiger, MD, PhD.

TABLE E1. Excerpts from eye care providers' reports of cataract or posterior findings, CAMP trial treatment group, and use of ICS and prednisone during any phase of CAMP

Reports including posterior findings
Budesonide group
1. Early PSCs in the right eye greater than the left, off axis so they are not currently affecting vision (per optometrist). Trace amount of PSC cataract on the right lens, as well as a Mittendorf dot on the right lens posteriorly; left lens is clear (per ophthalmologist). Used ICS. Never used prednisone.
2. Dense PSC in left eye, visually significant, corrected by surgery (per ophthalmologist). Used ICS and prednisone.
3. Possible trace bilateral posterior lens Atextural changes@ (per optometrist); Aminuscule@ right-sided posterior subcapsular cataract (PSC) less than 0.5 mm in diameter, not visually significant (per ophthalmologist). Used ICS and prednisone.
4. Congenital flecks in both eyes, sutures not opacified but more prominent than expected - both eyes; very early posterior subcapsular change - both eyes; my overall impression is these changes look more congenital than acquired; not affecting vision (per ophthalmologist #1). Entirely normal eye examination at this time; lenticular findings noted at previous examination are classically congenital (per ophthalmologist #2). Used ICS and prednisone.
5. 1+ anterior, 2+ posterior subcapsular - both eyes (per optometrist). Used ICS and prednisone.
Randomized to nedocromil
6. Trace PSC - both eyes (per optometrist). Never used ICS. Never used prednisone.
7. Hint of PSC (very, very subtle) - both eyes (per ophthalmologist). Used ICS and prednisone.
Randomized to placebo
8. Posterior subcapsular, grade 1, with decreased visual acuity - both eyes (per optometrist). Used ICS and prednisone.
9. Minimal posterior subcapsular opacity, irregular in shape, does not interfere with vision - both eyes (per optometrist). No cataracts (per ophthalmologist). Used ICS and prednisone.
10. Right eye - 1 small circular opacity posterior subcapsular, congenital; left eye - 2 small opacities - nuclear, congenital (per optometrist). Never used ICS. Used prednisone.
11. Right eye - no findings; left eye - posterior opacity and 2 cortical spokes (per optometrist). Used ICS and prednisone.
12. Right eye - slight lamellar and post subcapsular haze; left eye - slight lamellar and sutural opacities (per optometrist). Never used ICS. Used prednisone.
Reports not including posterior findings
Randomized to budesonide
13. Small spot of congenital cataract in right eye (per optometrist). Used ICS and prednisone.
14. Trace cortical and fetal opacities bilaterally and possible trace haze to back of right lens (per optometrist). Used ICS and prednisone.
Randomized to nedocromil
15. Pinpoint nuclear cataract, not posterior subcapsular (congenital?) - both eyes (per optometrist). Used ICS and prednisone.
Randomized to placebo
16. Right eye - no findings; left eye - very mild radial cataract (per optometrist). Used ICS and prednisone.