

Association of Pediatric Atopic Dermatitis and Cataract Development and Surgery

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IMPORTANCE There is a paucity of data addressing the risk of cataract development in pediatric patients with atopic dermatitis (AD).

OBJECTIVE To investigate the association of AD with subsequent cataract development and cataract surgery in a Korean pediatric population.

DESIGN, SETTING, AND PARTICIPANTS This population-based retrospective longitudinal cohort study used nationally representative data from the Korean National Health Insurance Service database from 2002 to 2013. Incident AD cases, consisting of patients younger than 20 years with AD and severe AD and were matched to 4 controls each using propensity score derived from age, sex, residential area, and household income.

MAIN OUTCOMES AND MEASURES Incidence probabilities of cataract development and cataract surgery between the AD group and controls were compared using Kaplan-Meier methods and log-rank tests. Cox proportional hazard models were fitted for cataract and cataract surgery to determine the risk factors in the matched cohort.

RESULTS Of 34 375 patients with incident AD (16 159 girls [47%]; mean [SD] age, 3.47 [4.96] years), there were 3734 severe AD cases (10.9%) with 137 500 matched controls. Development of cataracts was not different between the AD and control groups, (0.216% vs 0.227%; 95% CI, −0.041% to 0.063%; $P = .32$) or between the severe AD cohort and their controls (0.520% vs 0.276%; 95% CI, −0.073% to 0.561%; $P = .06$). Cataract surgery was performed more frequently in the AD cohort than in the control group (0.075% vs 0.041%; 95% CI, 0.017%-0.050%; $P = .02$) and in the severe AD cohort compared with their controls (0.221% vs 0.070%; 95% CI, 0.021%-0.279%; $P = .03$). Severe AD was associated with both development of cataract (adjusted hazard ratio, 1.94; 95% CI, 1.06-3.58, $P = .03$) and requirement for cataract surgery (adjusted hazard ratio, 5.48; 95% CI, 1.90-15.79, $P = .002$).

CONCLUSIONS AND RELEVANCE Absolute risk of cataract was rare, with or without AD, even after 10 years of observation. However, our results suggest that pediatric patients with AD have an increased risk for cataracts requiring surgery and that disease severity may increase the risk for cataract development and cataract surgery.

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← Invited Commentary

+ Supplemental content

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Atopic dermatitis (AD) is a common chronic inflammatory skin disease of childhood, affecting 10% to 20% of children in industrialized countries.^{1,2} Approximately 85% of all AD cases begin before age 5 years.¹ Patients with AD are frequently predisposed to ocular complications, such as blepharitis, keratoconjunctivitis, keratoconus, rhegmatogenous retinal detachment, and cataract.^{3,4} Atopic dermatitis has been associated with pathognomonic shield-shaped anterior subcapsular cataracts as well as posterior subcapsular cataracts.⁵ Childhood cataracts can lower the quality of sensory information during sensitive periods of visual system development. However, there is a paucity of data addressing the association between AD and subsequent cataract development in a population-based longitudinal study.⁶⁻¹⁵ To our knowledge, only a 2017 Danish study has revealed this association in an adult population; individuals with AD younger than 50 years are at increased risk of developing cataract and those 50 years or older are not.¹⁶ We therefore sought to elucidate the association between AD and subsequent cataract development in a nationwide, pediatric general population using the National Health Insurance Service–National Sample Cohort (NHIS-NSC) in Korea.

Methods

Study Population

This study was approved by the institutional review board at Seoul National University Bundang Hospital, and requirement for informed consent was waived by the institutional review board. The study complied with the guidelines of the Declaration of Helsinki.¹⁷ The study began in March 2017 and ended in November 2017. Analyses began in April 2017.

We used the NHIS-NSC database for this study. The NHIS is a single, compulsory medical insurance program in South Korea that started in 1977 and achieved universal coverage by 1989.¹⁸⁻²⁰ Therefore, the NHIS contains all information regarding health care use in Korea. The NHIS-NSC database consists of a random sample of 1 025 340 Korean residents, equivalent to approximately 2.2% of the Korean population in 2002. The database contains claims data over 12 years (2002 to 2013) for diagnoses, procedures, prescription records, demographic information, direct medical costs, and mortality.²⁰ The diagnosis was coded according to the *Korean Classification of Disease, Sixth Edition* (a version of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, adapted for the Korean health care system; a list of diagnostic codes used in this article are provided in eTable 1 in the Supplement). A validation study for the NHIS database showed the overall positive predictive value of this diagnosis system as 83.4%, comparing the diagnoses between the database and patients' medical record.²¹ Detailed information regarding NHIS and the database has been reported elsewhere.^{20,22-29} The database is open to any researcher whose study protocols are approved by the official review committee.

Eligibility Criteria

We defined a cohort consisting of patients with incident AD and matched controls to compare the risk of cataract development

Key Points

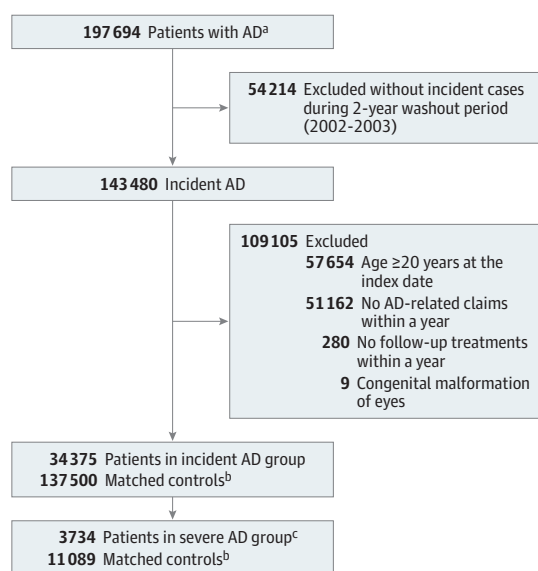
Question Is atopic dermatitis associated with cataract development or cataract surgery in the pediatric population?

Findings In this retrospective longitudinal study of 34 375 pediatric patients with atopic dermatitis, no differences were identified in the incident probability of cataract between the atopic dermatitis cohort and the control group. However, cataract surgery was performed more frequently in the atopic dermatitis cohort than in the control group.

Meaning These data suggest cataract development is quite rare in pediatric patients with atopic dermatitis, but they are at increased risk of undergoing cataract surgery.

between the 2 groups. First, we identified all patients with AD by using the relevant diagnostic code. The index date was defined as the earliest claim related to the AD diagnostic code. We considered index date as the incident time. To exclude patients with preexisting AD, we excluded individuals with index dates in the first 2 years (2002 to 2003) of the study period. Thus, all remaining patients with AD had a washout period of at least 2 years to ensure incidence of AD in the study period. Next, we confined the cohort to individuals younger than 20 years at the index date. Of these individuals, we included only those who within a year of the index date had at least 1 AD-related follow-up claim and received at least 1 of the following drugs for treatment of AD: oral antihistamines, topical corticosteroids, or topical calcineurin inhibitors (drug lists are provided in eTable 2 in the Supplement). Finally, we excluded individuals indicated with the diagnostic code of cataract before the index date of the study period. In addition, we excluded individuals diagnosed as having the following congenital diseases before the index date: congenital malformation of eyes including anophthalmos, microphthalmos, and macrophthalmos; congenital lens malformation; congenital malformation of anterior and posterior segments of eyes; and other congenital malformations of eyes. Among these individuals, we identified patients with severe AD on the basis of their use of prescribed drugs for treatment of AD in accordance with established guidelines.³⁰⁻³³ We classified patients as having severe AD when they had received any treatment within a year of the index date, including 1 or more treatments involving omalizumab, intravenous immunoglobulin, interferon γ , or rituximab and/or 2 or more weeks of cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, or systemic steroid administration. For the sensitivity analysis, we divided patients with incident AD in reference to administration of systemic steroids at least once within a year of the index date.

We matched 4 control individuals who did not have any AD-related claims throughout the study period to each patient with incident AD by estimated propensity scores after stratification in reference to the year of index date. Propensity scores were estimated by multiple logistic regression analysis in each year for all beneficiaries throughout the study period, regardless of outcomes. The model included age, sex, residential area, and household income in each study year. Eligibility criteria are summarized in Figure 1.

Figure 1. Flow Diagram for Identifying the Incident Atopic Dermatitis (AD) Cohort

^a Patients were identified with an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code (L20) from the National Health Insurance Service-National Sample Cohort Database, which included a random sample of 1 025 340 Koreans with 12 years of claims (2002-2013).

^b Sex, age, residential area, and household income were variables used in propensity-based matching.

^c Patients in the severe AD group received any treatment within a year of the index date, including 1 or more treatments involving omalizumab, intravenous immunoglobulin, interferon γ , or rituximab and/or 2 or more weeks of cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, or systemic steroid administration.

Statistical Analysis

The primary outcome was incidence probabilities of newly diagnosed cataract and cataract surgery, which were defined by the relevant diagnostic codes and surgical codes, respectively. We plotted and compared Kaplan-Meier curves between the AD and control groups by the log-rank test. Censoring was defined by death and end of follow-up (December 31, 2013). The probability of development of cataract and cataract surgery every year throughout the 10 years of follow-up was computed by life-table analysis. We also performed survival analysis in the severe AD group to determine if the severity of AD had an influence on the probability of survival. In sensitivity analysis for evaluating the effects of systemic steroids on cataract and cataract surgery in patients with AD, we compared Kaplan-Meier curves between the AD with steroid and the AD without steroid subgroups using the log-rank test.

To evaluate factors affecting cataract and cataract surgery, we fitted Cox proportional hazard models adjusting for age, sex, residential region, household income, and comorbidities such as asthma and allergic rhinitis. Comorbidity was defined if individuals had at least 1 claim with the corresponding diagnostic code within 2 years before the index date. All statistical analyses were performed using SAS, version 9.3 (SAS Inc) and R programming, version 3.1.0 (The R Foundation for

Statistical Computing). All reported *P* values are 2-sided, and *P* values were not adjusted for multiple analyses. A *P* value less than .05 indicated significance.

Results

We included a total of 34 375 patients with incident AD (16 159 girls [47%]; mean [SD] age, 3.47 [4.96] years) and 137 500 matched controls (64 892 girls [47%]; mean [SD] age, 3.80 [4.90] years) in the analyses. Among these, 3734 patients (1571 girls [42%]; mean [SD] age, 4.23 [5.68] years) were classified in the severe AD group; their matched control group included 11 089 individuals (4659 girls [42%]; mean [SD] age, 4.55 [5.50] years). Baseline characteristics of the AD cohort and control groups are summarized in eTable 3 in the [Supplement](#). There was no difference in age, sex, residential region, household income, or comorbidities between the AD and control groups.

Incidence Probability of Cataract

Forty-two of 34 375 patients with AD (0.12%) and 195 of 137 500 controls (0.14%) were newly diagnosed as having cataract. There was no difference in the incidence probability of cataract development between the AD and control groups (0.099% vs 0.138%; 95% CI, 0.036%-0.040% at 5 years and 0.216% vs 0.227%; 95% CI, -0.041% to 0.063% at 10 years; *P* = .32; **Figure 2A**). In the severe AD group and their matched controls, 11 of 3734 patients with AD (0.29%) and 20 of 11 089 controls (0.18%) were newly diagnosed as having cataract. Similarly, there was no difference in the incidence probability of cataract development between the severe AD and control groups (0.235% vs 0.144%; 95% CI, 0.080%-0.101% at 5 years and 0.520% vs 0.276%; 95% CI, -0.073% to 0.561% at 10 years; *P* = .06; **Figure 2B**).

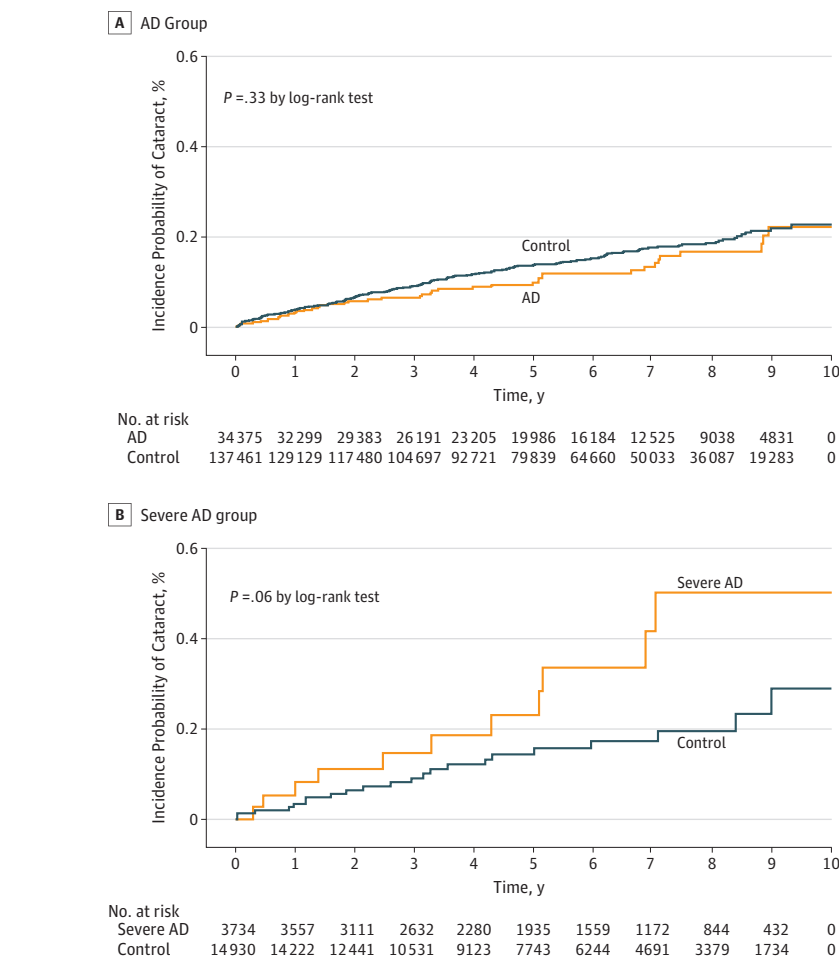
Incidence Probability of Cataract Surgery

Fourteen of 34 375 patients with AD (0.04%) and 26 of 137 500 controls (0.02%) underwent cataract surgery. Patients with AD underwent cataract surgery more frequently, compared with controls, as the incidence probability of cataract surgery was significantly higher in AD cohort than in the control group (0.033% vs 0.017%; 95% CI, 0.015%-0.016% at 5 years and 0.075% vs 0.041%; 95% CI, 0.017%-0.050% at 10 years; *P* = .02; **Figure 3A**). Similarly, in the severe AD group and their matched controls, patients with AD underwent cataract surgery more frequently compared with controls. Four patients with AD (0.11%) and 6 control individuals (0.05%) underwent cataract surgery. The incidence probability was significantly higher in patients with severe AD than in controls (0.034% vs 0.017%; 95% CI, 0.016%-0.018% at 5 years and 0.221% vs 0.070%; 95% CI, 0.021%-0.279%; *P* = .03; **Figure 3B**).

Sensitivity Analysis for Effects of Systemic Steroids

Of the 34 375 patients in the AD cohort, 28 820 patients (83.8%) were in the AD with steroid subgroup and 5555 patients (16.2%) were in the AD without steroid subgroup. There were no

Figure 2. Incidence Probability of Cataract



differences in the incidence probability of both cataract and cataract surgery (log-rank test, $P = .70$ and $P = .19$, respectively).

Cox Regression Model for Cataract Development

eTable 4 in the [Supplement](#) presents the results of Cox regression analysis for cataract development. After controlling for age, sex, residential region, household income, and comorbidities, the Cox regression model revealed an influence of severe AD on cataract. The adjusted hazard ratios of cataract development were 0.69 (95% CI, 0.47-1.01, $P = .06$) in the non-severe AD group and 1.95 (95% CI, 1.06-3.58, $P = .03$) in the severe AD group, compared with controls.

Cox Regression Model for Cataract Surgery

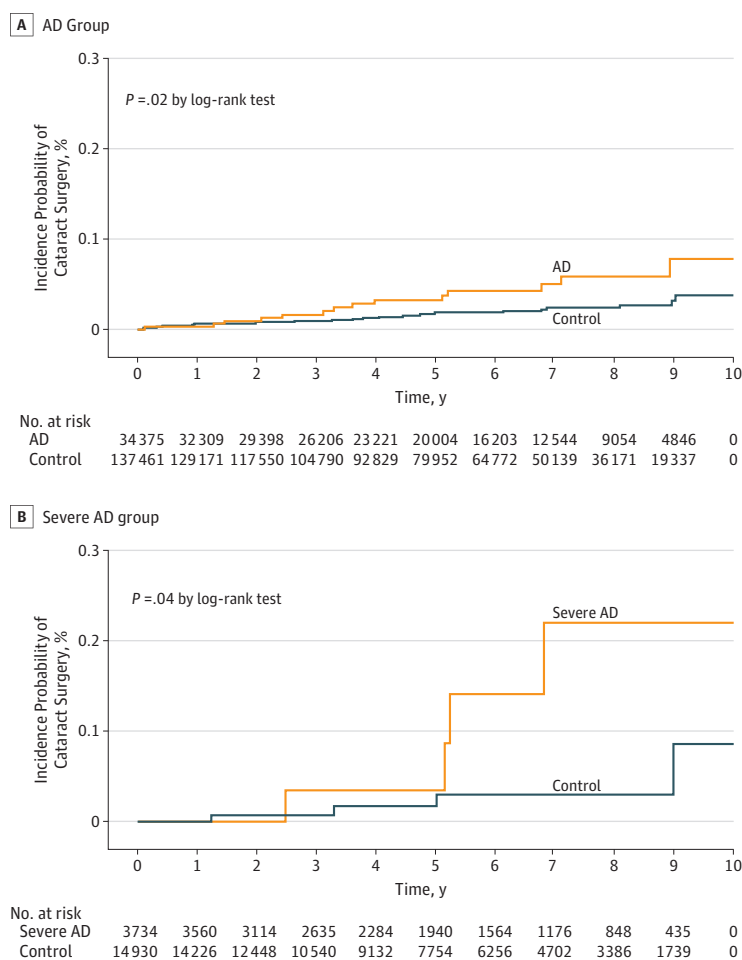
eTable 5 in the [Supplement](#) presents the results of Cox regression analysis for cataract surgery. After controlling for age, sex, residential region, household income, and comorbidities, the Cox regression model revealed an influence of severe AD on cataract surgery. The adjusted hazard ratios of cataract surgery were 1.61 (95% CI, 0.77-3.35, $P = .20$) in the nonsevere AD group and 5.48 (95% CI, 1.90-15.79, $P = .002$) in the severe AD group, compared with controls.

Discussion

The present study is a nationwide, population-based study to investigate the risk of cataract development and requirement for cataract surgery in patients with AD among the general pediatric population. Children with AD are at an increased risk of cataract development, which may require surgical treatment, compared with those without AD, and disease severity may increase the risk for cataract and cataract surgery. However, it is noteworthy that the incidence of cataract development was rare with or without AD, even after 10 years of observation; the incidence of cataract surgery was much rarer.

The association of AD with cataract has been reported since 1914 as dermatogenous cataract, which includes cataracts not only associated with AD but with several other dermatoses.¹³ Rather, atopic diseases-related cataract has been referred to as atopic cataract.^{7,9,12-14,34} Historically, atopic cataract occur in about 5% to 38% of patients with AD.¹²⁻¹⁴ However, most of these studies are hospital-based and conducted within a single hospital, which might be influenced by selection bias.^{6,12-14} The present study estimated the incidence probabilities of cataract and

Figure 3. Incidence Probability of Cataract Surgery



Cataract surgery was performed more frequently in the (A) atopic dermatitis (AD) cohort than in the control group (0.075% vs 0.041%, $P = .02$) and in the (B) severe AD cohort, compared with their controls (0.221% vs 0.070%, $P = .03$).

cataract surgery by the use of a nationwide, population-based, incident AD cohort in a longitudinal manner. In our results, the incidence probability of cataract was 0.216% in patients with AD and 0.520% in patients with severe AD at 10-year follow-up, which were lower than those reported in previous studies.¹²⁻¹⁴ Understandably, among these, only a small number of patients with AD underwent cataract surgery (0.075% in patients with AD and 0.221% in patients with severe AD at 10-year follow-up). Even considering the possibility of underdiagnoses, the threat of cataract development in children with AD is rather exaggerated.

Although the precise pathogenic mechanisms for development of cataracts in patients with AD remain elusive, clinical severity of AD,^{14,16,35} oxidative stress by free radicals,³⁶ and corticosteroid therapy^{14,37} are the main postulated pathogenic mechanisms. The Cox regression model in the present study revealed an influence of severe AD on cataract development and cataract surgery in pediatric patients with AD after controlling for age, sex, residential region, household income, and comorbidities. We performed a sensitivity analysis, comparing AD with and without the use of any systemic steroids within 1 year after AD diagnosis, to assess the effect of steroid use on cataract development and progres-

sion in patients with severe AD.^{15,37,38} Between groups, incidence probabilities of cataract or cataract surgery did not differ, suggesting disease severity as a likely pathogenic mechanism of cataract development in patients with AD. Further investigation is warranted to determine the pathogenesis of cataract suggested in this study that had inherent limitations of being a retrospective epidemiologic study using the claims database.

Limitations and Strengths

Our study has certain limitations. First, we might have underestimated the cataract incidence in pediatric patients with AD. We identified cataract patients using claims of cataract-related health care use and therefore could not include asymptomatic patients who did not have symptoms of cataract at presentation. Therefore, our data should be viewed as the incidence probability of clinically diagnosed cataract cases. Second, the diagnostic codes in the claims data may not be completely accurate; we could not validate the diagnosis of cataract by reviewing the medical records. However, we also evaluated the incidence probability of cataract surgery to reduce selection bias, as the included cases could be exclusive to vision-threatening cataract. Third, neither the type of

cataract in the AD group, nor the type of cataract in the control population, could be identified. This is a weakness, as non-progressive cataract types in control children ultimately may not require surgical intervention, therefore increasing the surgery rate in the AD group. In addition, we could not obtain precise information on the use of steroids such as dose, location, and administration route. Thus, we could not elucidate the exact pathogenic mechanism of cataract formation in patients with AD. Finally, our study lacked standardization of clinical features and may have encountered interobserver variations in the diagnosis of cataract, which is inherent to studies using a claims database.

Nevertheless, childhood cataract is a rare disease, and the cases included in our study with diagnostic codes are likely to have cataracts. Furthermore, for accuracy of AD diagnosis, we only included individuals who had received at least 1 drug for the treatment of AD within a year of the

index date. The use of an operational definition may be one of the strengths of our study.

Conclusions

In this population-based cohort study, we found that the absolute risk of cataract development in pediatric patients with AD was rare, even after 10 years of observation, and that the risk of requiring cataract surgery was much rarer. However, pediatric patients with AD exhibit an increased risk of cataract development, which may require surgical treatment; disease severity may increase the risk for cataract development and the associated requirement for cataract surgery. Although cataract is a manageable complication, physicians should closely monitor cataract development in children with AD, especially in cases of severe AD.

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Acquisition, analysis, or interpretation of data: Jeon, Byun, Hyon, S. Park.

Drafting of the manuscript: Jeon, S. Park.

Critical revision of the manuscript for important intellectual content: All authors.

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Study supervision: K. Park, S. Park.

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Supplementary Online Content

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eTable 1. List of diagnostic codes used for defining subjects

eTable 2. Drug lists used for defining atopic dermatitis

eTable 3. Baseline characteristics of atopic dermatitis cohort and control group

eTable 4. Cox analysis-derived hazard ratios (HRs) and 95% confidence intervals (CIs) of cataract development associated with atopic dermatitis (AD) and its covariates

eTable 5. Cox analysis-derived hazard ratios (HRs) and 95% confidence intervals (CIs) of cataract surgery associated with atopic dermatitis (AD) and its covariates

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. List of diagnostic codes used for defining subjects

Diagnoses	Code numbers in KCD-6^a
Atopic dermatitis	L20
Cataract	H25, H26
Congenital malformation of eyes (anophthalmos, microphthalmos, and macrophthalmos)	Q11
Congenital lens malformation	Q12
Congenital malformation of anterior segment of eyes	Q13
Congenital malformation of posterior segment of eyes	Q14
Other congenital malformations of eyes	Q15
Cataract surgery	S5110, S5111, S5112, S5119
Asthma	J45.0, J45.9
Allergic rhinitis	J30.1, J30.2, J30.3, J30.4

^aThe diagnosis was coded according to the Korean Classification of Disease, 6th edition (KCD-6, a version of the International Classification of Diseases, 10th edition, adapted for the Korean healthcare system).

eTable 2. Drug lists used for defining atopic dermatitis

Classification	Drug
Oral antihistamine	azelastine
	bepotastine
	cetirizine/levocetirizine
	chlorpheniramine maleate
	clemastine
	desloratadine
	ebastine
	emedastine
	epinastine
	fexofenadine
	hydroxyzine
	ketotifen fumarate
	loratadine
	mequitazine
	mizolastine
	montelukast
	olopatadine
	oxatomide
	pemirolast
	piprinhydrinate
	pranlukast
	triprolidine
	zafirlukast
Topical corticosteroid	amcinonide
	betamethasone valerate
	budesonide
	clobetasol propionate
	clobetasone butyrate
	desonide
	desoxymethasone
	dexamethasone propionate
	diflorasone diacetate
	difluocortolone valerate
	fluocinolone acetonide
	fluocinonide

Topical corticosteroid (continued)	fluticasone propionate
	halcinonide
	hydrocortisone acetate
	hydrocortisone butyrate
	methylprednisolone aceponate
	mometasone furoate
	prednicarbate
	prednisolone valeroacetate
Topical calcineurin inhibitor	triamcinolone acetonide
	pimecrolimus
	tacrolimus

eTable 3. Baseline characteristics of atopic dermatitis cohort and control group

	AD cohort, No. (%)	Control group, No. (%)
Total No.	34,375	137,500
Age		
0	11308 (32.90)	45232 (26.32)
1-4	14236 (41.41)	56944 (33.13)
5-9	3935 (11.45)	15740 (9.16)
10-14	2673 (7.78)	10704 (6.23)
15-19	2223 (6.47)	8880 (5.17)
Sex		
Male	18216 (52.99)	72608 (52.81)
Female	16159 (47.01)	64892 (47.19)
Residential region		
Seoul, Incheon	9139 (26.59)	36565 (26.59)
Gyeonggi, Gangwon	10083 (29.33)	40222 (29.25)
Gyeongsang	7580 (22.05)	30418 (22.12)
Chungcheong	3661 (10.65)	14596 (10.62)
Jeolla, Jeju	3912 (11.38)	15699 (11.42)
Household income		
≤40%	7244 (21.07)	29020 (21.11)
50-80%	18567 (54.01)	74244 (54.00)
>90%	8564 (24.91)	34236 (24.90)
Comorbidity		
Asthma	8477 (24.66)	47630 (34.64)
Allergic rhinitis	13352 (38.84)	71432 (51.95)

AD = atopic dermatitis.

eTable 4. Cox analysis-derived hazard ratios (HRs) and 95% confidence intervals (CIs) of cataract development associated with atopic dermatitis (AD) and its covariates

Variables		Events(n)	HR (95% CI)	P value ^a
AD	No	137,500	1.00	
	Non-severe AD	30,641	0.69 (0.47 - 1.01)	.06
	Severe AD	3,734	1.95 (1.06 - 3.58)	.03
Age	0	56,540	1	
	1-4	71,180	2.16 (1.45 - 3.22)	<.001
	5-9	19,675	2.29 (1.42 - 3.37)	<.001
	10-14	13,377	2.63 (1.60 - 4.33)	<.001
	15-19	11,103	3.99 (2.47 - 6.44)	<.001
Sex	Male	90,824	1	
	Female	81,051	3.99 (2.47 - 6.44)	.93
Residential region	Seoul, Incheon	45,704	1	
	Gyeonggi, Gangwon	50,305	1.67 (1.20 - 2.34)	.003
	Gyeongsang	37,998	0.98 (0.65 - 1.46)	.91
	Chungcheong	18,257	1.20 (0.75 - 1.94)	.44
	Jeola, Jeju	19,611	0.92 (0.55 - 1.52)	.73
Household income	≤40%	36,264	1	
	50-80%	92,811	0.79 (0.56 - 1.10)	.16
	>90%	42,800	1.31 (0.92 - 1.85)	.13
Comorbidity				
Asthma	No	115,768	1	
	Yes	56,107	1.24 (0.91 - 1.69)	.17
Allergic rhinitis	No	87,091	1	
	Yes	84,784	0.69 (0.52 - 0.92)	.01

AD = atopic dermatitis; CI = confidence interval; HR = hazard ratio

^a Model was adjusted for AD, age, sex, residential region, household income and comorbidity in Cox proportional hazards regression.

eTable 5. Cox analysis-derived hazard ratios (HRs) and 95% confidence intervals (CIs) of cataract surgery associated with atopic dermatitis (AD) and its covariates

Variables		Events(n)	HR (95% CI)	P value ^a
AD	No	137,500	1.00	
	Non-severe AD	30,641	1.61 (0.77 - 3.35)	.20
	Severe AD	3,734	5.48 (1.90 - 15.79)	.002
Age	0	56,540	1	
	1-4	71,180	0.73 (0.29 - 1.84)	.50
	5-9	19,675	0.91 (0.28 - 2.95)	.86
	10-14	13,377	2.76 (1.13 - 6.74)	.02
	15-19	11,103	2.05 (0.71 - 5.97)	.18
Sex	Male	90,824	1	
	Female	81,051	0.73 (0.39 - 1.38)	.33
Residential region	Seoul, Incheon	45,704	1	
	Gyeonggi, Gangwon	50,305	2.98 (0.98 - 9.15)	.06
	Gyeongsang	37,998	3.77 (1.23 - 11.58)	.02
	Chungcheong	18,257	1.84 (0.41 - 8.23)	.42
	Jeolla, Jeju	19,611	3.80 (1.11 - 13.04)	.03
Household income	≤40%	36,264	1	
	50-80%	92,811	0.49 (0.24 - 1.02)	.06
	>90%	42,800	0.62 (0.27 - 1.41)	.25
Comorbidity				
Asthma	No	115,768	1	
	Yes	56,107	0.84 (0.34 - 2.09)	.70
Allergic rhinitis	No	87,091	1	
	Yes	84,784	0.57 (0.27 - 1.22)	.14

AD = atopic dermatitis; CI = confidence interval; HR = hazard ratio.

^a Model was adjusted for AD, age, sex, residential region, household income and comorbidity in Cox proportional hazards regression.