Age-Related Cataract Is Associated with Elevated Serum Immunoglobulin E Levels in the South Korean Population: A Cross-Sectional Study

Tae Keun Yoo¹, Sun Woong Kim²*, Kyoung Yul Seo¹**

¹ Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, Seoul, South Korea, ² Department of Ophthalmology, Yonsei University Wonju College of Medicine, Wonju, South Korea

* These authors contributed equally to this work.
* eyedockim@yonsei.ac.kr (SWK); seoky@yuhs.ac (KYS)

Abstract

Background
Previous research has suggested that immunoglobulin E (IgE)-mediated events lead to several chronic diseases. We investigated the association between allergic conditions and age-related cataracts in the South Korean adult population.

Methods
A cross-sectional study was performed using data obtained from 1,170 participants aged 40 years or older who were enrolled in the Korean National Health and Nutrition Examination Survey 2010. Multivariable logistic regression was used to examine the relationship between age-related cataracts and allergic conditions, including total serum IgE and allergen-specific serum IgE levels, after adjustment for potential confounders (age, sex, alcohol consumption, smoking, sun exposure, blood pressure, plasma glucose and cholesterol levels, as well as histories of asthma, atopic dermatitis, and rheumatoid arthritis).

Results
After adjusting for potential confounders, the odds ratio (OR) for age-related cataract was greater in participants with higher total serum IgE levels (OR = 1.37; P = 0.044). In particular, increased IgE levels were significantly associated with nuclear cataract (OR = 1.42; P = 0.032). However, allergen-specific serum IgE levels did not differ significantly between groups. In the trend analysis, no significant relationship was observed between serum IgE and any type of age-related cataract.
Conclusion

Increased total serum IgE level is independently associated with age-related cataracts after adjustment for confounding factors.

Introduction

Cataract, defined as opacity of the crystalline lens, is the most common cause of visual loss worldwide [1]. Moreover, the prevalence of age-related cataract will increase rapidly as society ages; this will produce a huge socioeconomic burden worldwide. Nonetheless, the exact mechanisms that lead to age-related cataract remain unclear. In recent years, research has focused on the systemic conditions that increase the risk of age-related cataract. In particular, glycation and oxidative change of lens proteins as a result of elevated glucose levels in serum and aqueous humor has been recognized as a major pathophysiological process in cataract formation [2]. Systemic oxidative stress is also a risk factor [3]. Conversely, several population-based studies have indicated that various antioxidants prevent cataract development [4]. Additionally, increased prevalence of cataract has been reported in patients with history of smoking, hypertension, steroid use, and celiac disease [5,6]. Socioecomic status was also associated with age-related cataract [7].

Immunoglobulin E (IgE) is an antibody that binds to Fc (fragment, crystallizable) receptors, which are mostly found on the surface of mast cells [8]. It plays a key role in the signaling response to allergens. The binding of IgE to the Fc receptor activates mast cell degranulation, as well as the release of mediators such as cytokines, chemokines, histamine, proteoglycan, and mast cell protease. These mediators induce a reaction that is typical of hypersensitivity: vascular leakage, vasodilation, and airway constriction [9]. Clinically, increased IgE levels have been found in patients with atopic dermatitis, asthma, and hay fever [10]. In more recent research, increased IgE has also been associated with several chronic diseases, including rheumatoid arthritis [11], atherosclerosis [12], ischemic heart disease [9], and diabetes mellitus [13,14]. In particular, the inflammatory mediators released from mast cells may increase capillary permeability and joint inflammation in patients with rheumatoid arthritis, and they may trigger vasoconstriction and endothelial cell remodeling in patients with atherosclerosis [15,16]. Moreover, a previous report have suggested that these mediators increase cytokine-induced insulin resistance and impair insulin secretion [13].

It is well-known that anterior and posterior subcapsular cataracts are a common ocular complication of atopic dermatitis [17]. However, the association between age-related cataract and allergic conditions remains unclear—although previous studies have suggested that systemic inflammation is involved in the progression of age-related cataract [18,19]. Because the IgE-mediated immune response may be a major trigger of systemic inflammation, we hypothesized that serum IgE level is associated with the development of age-related cataract.

In the present study, we investigated whether increased serum IgE is associated with the prevalence of age-related cataract after adjustment for well-known risk factors (age, sex, body mass index [20], smoking [21], alcohol use [22], sun exposure [23], blood pressure [5], plasma glucose level [2], cholesterol level [24], and history of chronic diseases associated with steroid use [25]).
Methods

All analyses were based on the Korean National Health and Nutrition Examination 2010 (KNHANES; available online at http://knhanes.cdc.go.kr). The study protocol was approved by the institutional review board of the Korean Center for Disease Control and Prevention (IRB Number: 2010-02CON-21-C). All participants signed forms consenting to the use of their health information in the study. The KNHANES 2010 was a nationwide, population-based, cross-sectional survey conducted by the Division of Chronic Disease Surveillance of the Korea Centers for Disease Control and Prevention [26]. All participants were randomly selected from among 192 surveys conducted at 131 locations using stratified sampling in which the following factors were considered: population, gender, age, regional area, and type of residential area. The KNHANES itself comprised health records that were based on a health interview, a health examination, and a nutrition survey. Specially, the 2010 KNHANES survey gathered information on total and allergen-specific serum IgE [27].

A flow diagram of the inclusion and exclusion procedure is shown in Fig 1. A total of 8,958 participants were enrolled in the KNHANES 2010. However, we excluded from the present study (1) those under 40 years of age, in whom age-related cataracts are not a concern, (2) those without either a health interview or examination data (n = 6,800), (3) participants in whom IgE level was not measured (n = 2,814), and (4) subjects who had not undergone an eye examination (n = 14). Ultimately, 1,170 participants were eligible for the current analysis.

A structured eye examination was performed using a slit-lamp (Haag-Streit model BQ-900; Haag-Streit AG, Koeniz, Switzerland) to evaluate the participants’ cataract status [28]. The standard Lens Opacities Classification System III (LOCS III) was used to categorize the type of cataract.

![Flowchart of participant selection from the Korean National Health and Nutrition Examination Survey 2010.](https://example.com/flowchart.png)

doi:10.1371/journal.pone.0166331.g001
cataract. Cataracts were compared with standard photographs and classified as cortical (LOCS III score ≥2 for cortical cataracts), nuclear (LOCS III score ≥4 for nuclear opalescence or nuclear color), anterior subcapsular (LOCS III score ≥2 for anterior subcapsular cataracts), posterior subcapsular (LOCS III score ≥2 for posterior subcapsular cataracts), or mixed type (more than one cataract type per eye). Pseudophakic eyes were categorized into the same group as those that had undergone previous cataract surgery. To analyze risk factors associated with each type of age-related cataract, we defined the cataract patients into subtypes. Participants who had a predominantly cortical cataract in at least one eye with no other type of cataract in either eye were defined as having a pure cortical cataract. Participants with a nuclear cataract or an anterior and posterior capsular cataract were defined in a similar manner. Participants who had different cataract subtypes in each eye were defined as having mixed cataract. All ophthalmologic examinations were performed by 154 well-trained ophthalmologists or ophthalmology residents. To reduce inter-observer variation, participating investigators were periodically trained by acting staff members of the National Epidemiologic Survey Committee of the Korean Ophthalmologic Society. All ophthalmic investigators were masked to other data, including serum IgE level. The quality of the survey and cataract evaluation was verified by the Epidemiologic Survey Committee of the Korean Ophthalmologic Society [7].

Demographic information on traditional cataract-related risk factors was obtained during the health interview. Specifically, each participant completed a questionnaire in which they provided information on age, smoking status, alcohol use, sun exposure, and medical history. Blood pressure was also measured by the health professionals. Sunlight exposure time was evaluated by a multiple-choice question with the following answer options: <2 hours, 2–5 hours, and >5 hours per day. Fasting blood samples of individual participants were collected to measure serum biomarkers (fasting glucose, total cholesterol, triglyceride, and serum IgE). The blood samples were immediately refrigerated and transported to the Central Testing Institute in Seoul, South Korea. Levels of total serum IgE and antigen-specific IgE against Dermatophagoides farinae, cockroach, and dog allergen were also examined using an ImmunoCAP100 kit (Phadia, Uppsala, Sweden) and a 1470 WIZARD gamma-Counter analyzer (PerkinElmer, Turku, Finland) [27]. The upper limits of detectable total IgE and antigen-specific IgE were 5000 kU/L and 100 kU/L, respectively. Total IgE levels of more than 100 kU/L were categorized into the “increased IgE” group, and participants with allergen-specific IgE levels of 0.35 kU/L or more were defined as sensitized [29].

The characteristics of the participants in terms of cataract status were compared using the χ² test (for categorical data) or the Wilcoxon rank-sum test (for continuous data). To assess the association between cataract and increased IgE levels and sensitization to specific antigens, we used multivariable logistic regression to estimate the respective odds ratio (OR). The estimated ORs were calculated in the following ways: crude OR, in which no adjustment was made for potential confounders; Model 1, wherein the data were adjusted for age, sex, body mass index [20], smoking [21], alcohol use [22], and sun exposure [23] (Model 1); Model 2, wherein data were adjusted for all the variables in Model 1 plus factors associated with metabolic and chronic diseases (systolic blood pressure [5], fasting plasma glucose [2], and total cholesterol [24], as well as asthma [25], atopic dermatitis [17], and rheumatoid arthritis [30] where there is a high probability of steroid use). As the 2010 KNHANES did not measure cumulative steroid dose, the adjustment for steroid use was performed using only disease status data for asthma, atopic dermatitis, and rheumatoid arthritis.

To avoid collinearity between the confounders (systolic and diastolic pressure, or total cholesterol and triglyceride), we selected systolic blood pressure and total cholesterol level as covariates. When calculating the correlation matrix of all covariates, there was no multi-collinearity problem (all pairwise Pearson’s correlations: r < 0.5). We considered P-values < 0.05 as
statistically significant. All statistical analyses were completed using the SPSS Statistics 21.0 software (IBM SPSS Inc., Chicago, IL, USA).

**Results**

Ultimately, a total of 1,170 participants were included in this study. In Table 1, the general characteristics of the study participants are arranged according to their cataract status. Participants with age-related cataract were more likely to be older; they also drank alcohol more frequently and had higher systolic blood pressure, lower diastolic blood pressure, higher fasting plasma glucose, and higher total serum IgE.

| Table 1. Demographic and clinical characteristics of the study participants. |
|--------------------------|----------------|----------------|----------------|----------------|
|                          | Total participants (N = 1170) | Cataract or pseudophakia (N = 438) | No cataract (N = 732) | P-value |
| Age (years)              | 55.0 ± 9.4                  | 61.6 ± 8.2                  | 51.1 ± 7.8                  | <0.001  |
| Female (%)               | 582 (49.7)                  | 255 (51.4)                  | 357 (48.8)                  | 0.398   |
| BMI (kg/m²)              | 24.1 ± 2.9                  | 24.2 ± 3.2                  | 24.0 ± 2.8                  | 0.127   |
| House income             |                             |                             |                             |         |
| Very low (%)             | 247 (21.3)                  | 135 (31.3)                  | 112 (15.4)                  | <0.001  |
| Low (%)                  | 293 (25.3)                  | 112 (26.0)                  | 181 (24.9)                  |         |
| Moderate (%)             | 279 (24.1)                  | 92 (21.3)                   | 187 (25.8)                  |         |
| High (%)                 | 338 (29.2)                  | 92 (21.3)                   | 246 (33.9)                  |         |
| Education                |                             |                             |                             |         |
| Middle school            | 532 (46.0)                  | 274 (63.0)                  | 258 (35.7)                  | <0.001  |
| > High school            | 625 (54.0)                  | 161 (37.0)                  | 464 (64.3)                  |         |
| Region of residence      |                             |                             |                             |         |
| Urban (%)                | 898 (76.8)                  | 324 (74.0)                  | 574 (78.4)                  | 0.086   |
| Rural (%)                | 272 (23.2)                  | 114 (26.0)                  | 158 (21.6)                  |         |
| Smoking                  |                             |                             |                             |         |
| No smoking (%)           | 629 (53.8)                  | 242 (55.3)                  | 387 (52.9)                  | 0.066   |
| Ex-smoking (%)           | 264 (22.6)                  | 108 (24.7)                  | 156 (21.3)                  |         |
| Current smoking (%)      | 277 (23.7)                  | 88 (20.1)                   | 189 (25.8)                  |         |
| Alcohol use (≥1 drink/week, %) | 511 (43.7)                  | 162 (37.0)                  | 349 (47.7)                  | <0.001  |
| Sun exposure             |                             |                             |                             |         |
| ≤2 hours/day (%)         | 679 (57.9)                  | 239 (54.6)                  | 440 (60.0)                  | 0.051   |
| 2–5 hours/day (%)        | 299 (25.6)                  | 111 (25.3)                  | 188 (25.7)                  |         |
| >5 hours/day (%)         | 192 (16.4)                  | 88 (20.1)                   | 104 (14.2)                  |         |
| Asthma (%)               | 48 (4.1)                    | 21 (4.8)                    | 27 (3.7)                    | 0.365   |
| Atopic dermatitis (%)    | 35 (3.0)                    | 12 (2.7)                    | 23 (3.2)                    | 0.727   |
| Rheumatoid arthritis (%) | 40 (3.4)                    | 18 (4.1)                    | 22 (3.0)                    | 0.323   |
| SBP (mmHg)               | 122.8 ± 17.2                | 126.39 ± 17.0               | 120.7 ± 17.0                | <0.001  |
| DBP (mmHg)               | 77.5 ± 10.3                 | 76.7 ± 9.4                  | 77.9 ± 10.8                 | 0.036   |
| Fasting plasma glucose (mg/dL) | 101.3 ± 25.0                | 103.4 ± 24.6                | 100.1 ± 25.2                | 0.028   |
| Total cholesterol (mg/dL) | 193.7 ± 37.9                | 191.2 ± 37.5                | 195.3 ± 38.1                | 0.075   |
| Triglyceride (mg/dL)     | 147.8 ± 116.4               | 146.7 ± 90.1                | 148.4 ± 129.7               | 0.797   |
| Increased total serum IgE (%) | 550 (47.0)                  | 233 (53.2)                  | 317 (43.3)                  | <0.001  |

BMI, body mass index; DBP, diastolic blood pressure; IgE, immunoglobulin E; SBP, Systolic blood pressure.

doi:10.1371/journal.pone.0166331.t001
plasma glucose, and higher IgE levels. Fig 2 presents the prevalence of cataracts in terms of their LOCS status. The prevalence of cataracts or pseudophakia increased as the participants became older. Nuclear cataract was the most common type of cataract in the KNHANES 2010. The total prevalence of cataracts or pseudophakia among the study population was 34.7%. The cataract types and their prevalence rates were as follows: cortical cataract (7.6%), nuclear cataract (21.1%), anterior subcapsular cataract (0.6%), posterior subcapsular cataract (0.2%), and mixed cataract (4.5%). Table 2 shows the number of patients affected by each cataract type in each serum IgE concentration quartile. Patients in higher serum IgE quartiles had a significantly higher prevalence of nuclear cataract than those in lower serum IgE quartiles ($P$-value for linear trend = 0.018).

Table 3 presents the relationship between the various confounding factors and the risk of age-related cataract. Before adjustment, logistic regression showed that age, alcohol use, sun exposure (more than 5 hours per day), systolic blood pressure, diastolic blood pressure, fasting glucose level, and increased serum IgE level were risk factors for age-related cataracts. Increased serum IgE remained a significant risk factor after adjustment in Model 1 (OR = 1.36; $P$ = 0.048) and Model 2 (OR = 1.37; $P$ = 0.044). In contrast, sensitization to specific antigens, including *Dermatophagoides farinae*, cockroach, and dog, was not significantly associated with age-related cataract.

**Table 2. The prevalence of each cataract subtype in patients with various serum IgE levels.**

| Serum IgE quartile (kU/L) | P-value for $\chi^2$ test | P-value for linear trend |
|---------------------------|----------------------------|--------------------------|
| <35.0                     |                            |                          |
| 35.0–37.6                 |                            |                          |
| 37.7–267.0                |                            |                          |
| >267.0                    |                            |                          |
| Cortical cataract         | 12                         | 0.038                    |
| Nuclear cataract          | 51                         | 0.015                    |
| Anterior subcapsular cataract | 1                     | 0.740                    |
| Posterior subcapsular cataract | 1                     | 0.920                    |
| Mixed cataract            | 17                         | 0.554                    |
| Pseudophakia              | 6                          | 0.417                    |

**Fig 2. Prevalence of each cataract type within each age group in the Korean National Health and Nutrition Examination Survey 2010.**

doi:10.1371/journal.pone.0166331.g002

doi:10.1371/journal.pone.0166331.t002
The possible effects of socioeconomic status on the association between IgE and age-related cataract were also examined. Additional adjustments for household income and education had no effect on the associations reported above, which showed an age-related cataract OR of 1.41 in Model 1 (P = 0.028) and 1.42 in Model 2

### Table 3. Logistic regression analysis of the association between age-related cataracts and demographic or clinical factors.

|                          | Crude   | Model 1* | Model 2† |
|--------------------------|---------|----------|----------|
|                          | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Age (years)              | 1.16 (1.14–1.18) | <0.001 | 1.16 (1.14–1.18) | <0.001 | 1.16 (1.14–1.18) | <0.001 |
| Female                   | 1.11 (0.87–1.40) | 0.390  | 1.01 (0.64–1.61) | 0.921  | 1.04 (0.68–1.58) | 0.851  |
| BMI (kg/m²)              | 1.03 (0.99–1.07) | 0.116  | 0.99 (0.65–1.26) | 0.838  | 1.00 (0.95–1.05) | 0.992  |
| House income             |         |          |          |          |          |          |
| Very low                 | 1.00 (reference) |       | 1.00 (reference) |       | 1.00 (reference) |       |
| Low                      | 0.51 (0.34–0.72) | <0.001 | 1.09 (0.72–1.67) | 0.659  | 1.10 (0.72–1.84) | 0.644  |
| Moderate                 | 0.40 (0.28–0.58) | <0.001 | 1.47 (0.94–2.31) | 0.088  | 1.49 (0.95–2.35) | 0.081  |
| High                     | 0.31 (0.21–0.43) | <0.001 | 1.19 (0.76–1.85) | 0.428  | 1.19 (0.76–1.86) | 0.425  |
| Education                |         |          |          |          |          |          |
| ≤ Middle school          | 1.00 (reference) |       | 1.00 (reference) |       | 1.00 (reference) |       |
| > High school            | 0.32 (0.25–0.41) | <0.001 | 1.01 (0.72–1.39) | 0.968  | 1.01 (0.72–1.39) | 0.975  |
| Region of residence      |         |          |          |          |          |          |
| Urban                    | 1.00 (reference) |       | 1.00 (reference) |       | 1.00 (reference) |       |
| Rural                    | 1.27 (0.96–1.68) | 0.082  | 1.21 (0.86–1.70) | 0.274  | 1.21 (0.86–1.71) | 0.258  |
| Smoking                  |         |          |          |          |          |          |
| No smoking               | 1.00 (reference) |       | 1.00 (reference) |       | 1.00 (reference) |       |
| Ex-smoking               | 1.11 (0.82–1.48) | 0.496  | 1.00 (0.61–1.64) | 0.987  | 1.00 (0.61–1.64) | 0.991  |
| Current smoking          | 0.74 (0.55–1.00) | 0.054  | 0.94 (0.56–1.57) | 0.824  | 0.94 (0.56–1.57) | 0.816  |
| Alcohol use (>1 drinking/week) | 0.64 (0.50–0.82) | <0.001 | 0.91 (0.65–1.26) | 0.612  | 0.91 (0.65–1.27) | 0.588  |
| Sun exposure             |         |          |          |          |          |          |
| <2 hours/day             | 1.00 (reference) |       | 1.00 (reference) |       | 1.00 (reference) |       |
| 2–5 hours/day            | 1.08 (0.81–1.44) | 0.563  | 0.82 (0.58–1.16) | 0.274  | 0.82 (0.58–1.16) | 0.278  |
| >5 hours/day             | 1.55 (1.12–2.15) | 0.007  | 1.04 (0.70–1.53) | 0.842  | 1.03 (0.70–1.53) | 0.847  |
| Asthma                   | 1.31 (0.73–2.34) | 0.363  | 0.78 (0.38–1.61) | 0.514  | 0.78 (0.38–1.61) | 0.497  |
| Atopic dermatitis        | 0.86 (0.42–1.75) | 0.689  | 0.90 (0.38–2.12) | 0.821  | 0.90 (0.38–2.12) | 0.875  |
| Rheumatoid arthritis     | 1.37 (0.73–2.60) | 0.321  | 1.07 (0.50–2.27) | 0.858  | 1.06 (0.49–2.27) | 0.862  |
| SBP (mmHg)               | 1.02 (1.01–1.03) | <0.001 | 1.00 (0.99–1.01) | 0.904  | 1.00 (0.99–1.01) | 0.924  |
| DBP (mmHg)               | 0.99 (0.78–1.00) | 0.043  | 0.99 (0.87–1.01) | 0.400  | 0.99 (0.87–1.01) | 0.398  |
| Fasting plasma glucose (mg/dL) | 1.01 (1.00–1.01) | 0.030  | 1.00 (0.99–1.01) | 0.511  | 1.00 (0.99–1.01) | 0.491  |
| Total cholesterol (mg/dL) | 0.99 (0.99–1.00) | 0.076  | 0.99 (0.99–1.00) | 0.108  | 0.99 (0.99–1.00) | 0.103  |
| Triglyceride (mg/dL)     | 1.00 (0.99–1.00) | 0.814  | 1.00 (0.99–1.00) | 0.819  | 1.00 (0.99–1.00) | 0.894  |
| Increased total serum IgE| 1.48 (1.17–1.88) | 0.001  | 1.36 (1.00–1.85) | 0.048  | 1.37 (1.01–1.86) | 0.044  |
| Sensitization to specific allergen |         |          |          |          |          |          |
| Dermatophagoides farina | 1.07 (0.83–1.38) | 0.565  | 1.12 (0.82–1.53) | 0.466  | 1.12 (0.82–1.54) | 0.450  |
| Cockroaches              | 1.04 (0.77–1.39) | 0.804  | 0.86 (0.59–1.24) | 0.428  | 0.84 (0.58–1.22) | 0.387  |
| Dogs                     | 0.99 (0.55–1.77) | 0.974  | 0.89 (0.45–1.76) | 0.748  | 0.89 (0.45–1.78) | 0.761  |

BMI, body mass index; DBP, diastolic blood pressure; IgE, immunoglobulin E; SBP, Systolic blood pressure.

*Model 1 was adjusted for age, sex, body mass index, smoking, alcohol use, and sun exposure.

†Model 2 was adjusted for all of the factors in Model 1 and systolic blood pressure, fasting plasma glucose, total cholesterol, asthma, atopic dermatitis, and rheumatoid arthritis.

doi:10.1371/journal.pone.0166331.t003
(P = 0.028) in subjects with an increased IgE level. Therefore, the effect of socioeconomic status on the association between IgE and age-related cataract was minimal.

Multivariable logistic regression was performed in each cataract subtype group to examine the association of cataracts with both total and allergen-specific serum IgE levels. The OR results are listed in Table 4. In a univariate analysis, we found that participants with increased IgE levels had a significant risk of nuclear-type cataract (OR = 1.60; P = 0.001). Increased IgE remained a significant risk factor for nuclear cataract after adjustment for confounding factors in Model 1 (OR = 1.41; P = 0.036) and Model 2 (OR = 1.43; P = 0.032). Sensitization to specific antigens was not a significant risk factor for any type of cataract.

To explore the more specific association between IgE levels and age-related cataracts, we carried out additional analyses involving the quartiles of IgE level. The ORs for each quartile of serum IgE concentration, adjusted for the variables in the fully adjusted model (Model 2), are shown in Fig 3. The trend analysis showed no significant linear pattern in the relationship between serum IgE concentration and the risk of any type of cataract. However, the outcome for nuclear cataract showed a weak association with serum IgE level, although it was not statistically significant. Compared with the first IgE quartile, the adjusted ORs were 1.00, 1.49, and 1.36 in the second, third, fourth quartile, respectively (P for linear trend = 0.080). Subgroup analyses were also performed in each age group. As shown in Table 5, an increased IgE level did not significantly affect cataract prevalence in younger age groups (40 to 59 years).

### Table 4. Odds ratios for the association of each cataract type with total and allergen-specific serum IgE.

| Cataract Type | Increased total IgE | Sensitization to *Dermatophagoides farina* | Sensitization to Cockroaches | Sensitization to Dogs |
|---------------|---------------------|-------------------------------------------|-----------------------------|----------------------|
|               | OR (95% CI)         | P-value                                   | OR (95% CI)                 | P-value              |
| Cortical cataract |                    |                                           |                             |                      |
| Crude         | 1.35 (0.87–2.08)    | 0.175                                     | 1.11 (0.71–1.75)            | 0.636                | 0.85 (0.49–1.50)     | 0.592                | 0.23 (0.03–1.71)     | 0.153                |
| Model 1*      | 1.25 (0.78–2.01)    | 0.344                                     | 1.17 (0.72–1.89)            | 0.508                | 0.79 (0.44–1.43)     | 0.795                | 0.23 (0.03–1.75)     | 0.235                |
| Model 2†      | 1.26 (0.78–2.03)    | 0.333                                     | 1.18 (0.73–1.90)            | 0.500                | 0.79 (0.43–1.43)     | 0.792                | 0.24 (0.03–1.81)     | 0.168                |
| Nuclear cataract |                    |                                           |                             |                      |
| Crude         | 1.60 (1.20–2.12)    | 0.001                                     | 1.24 (0.93–1.67)            | 0.137                | 1.28 (0.91–1.79)     | 0.145                | 1.15 (0.59–2.24)     | 0.668                |
| Model 1*      | 1.41 (1.02–1.94)    | 0.036                                     | 1.24 (0.90–1.72)            | 0.185                | 1.14 (0.78–1.65)     | 0.483                | 1.05 (0.52–2.12)     | 0.885                |
| Model 2†      | 1.42 (1.03–1.96)    | 0.032                                     | 1.25 (0.90–1.74)            | 0.170                | 1.13 (0.78–1.65)     | 0.563                | 1.03 (0.51–2.08)     | 0.926                |
| Anterior subcapsular cataract |                   |                                           |                             |                      |
| Crude         | 0.84 (0.18–3.79)    | 0.826                                     | 0.33 (0.03–2.72)            | 0.301                | 0.65 (0.07–5.49)     | 0.699                | NA                   | NA                   |
| Model 1*      | 0.80 (0.15–4.20)    | 0.798                                     | 0.33 (0.03–2.93)            | 0.320                | 0.71 (0.07–6.52)     | 0.764                | NA                   | NA                   |
| Model 2†      | 0.82 (0.15–4.37)    | 0.817                                     | 0.29 (0.03–2.65)            | 0.273                | 0.69 (0.07–6.65)     | 0.749                | NA                   | NA                   |
| Posterior subcapsular cataract |                  |                                           |                             |                      |
| Crude         | 1.12 (0.07–18.69)   | 0.932                                     | NA                          | NA                   | NA                   | NA                   | NA                   | NA                   |
| Model 1*      | 1.95 (0.10–37.21)   | 0.655                                     | NA                          | NA                   | NA                   | NA                   | NA                   | NA                   |
| Model 2†      | 2.07 (0.10–41.15)   | 0.632                                     | NA                          | NA                   | NA                   | NA                   | NA                   | NA                   |
| Mixed cataract |                    |                                           |                             |                      |
| Crude         | 0.93 (0.53–1.61)    | 0.797                                     | 0.56 (0.29–1.08)            | 0.086                | 0.49 (0.20–1.16)     | 0.107                | NA                   | NA                   |
| Model 1*      | 0.76 (0.40–1.41)    | 0.389                                     | 0.59 (0.29–1.20)            | 0.149                | 0.41 (0.16–1.03)     | 0.060                | NA                   | NA                   |
| Model 2†      | 0.81 (0.43–1.53)    | 0.522                                     | 0.53 (0.26–1.10)            | 0.100                | 0.39 (0.15–1.04)     | 0.055                | NA                   | NA                   |

NA, not assessed (due to too low prevalence of each type of cataract).
*Model 1 was adjusted for age, sex, body mass index, smoking, alcohol use, and sun exposure.
†Model 2 was adjusted for all of the factors on Model 1 and systolic blood pressure, fasting plasma glucose, total cholesterol, asthma, atopic dermatitis, and rheumatoid arthritis.

doi:10.1371/journal.pone.0166331.t004
However, cataract patients tended to have increased total IgE levels in older age groups (≥60 years old).

**Discussion**

To our knowledge, this study was the first to evaluate the association between serum IgE levels and age-related cataracts in the general population. Our results demonstrated that study participants with increased total serum IgE levels had a significantly higher OR for age-related cataract after adjustment for confounding factors. In particular, increased IgE was significantly associated with nuclear cataract—the most common form of age-related cataract. However, neither of these findings was true of IgE sensitization to allergens in our regression models. The trend analysis of the ORs did not show a significant linear trend between the risk for age-related cataract and the serum total IgE quartiles. Since the analysis used data from a nationally representative sample of the population and was adjusted for a wide range of confounders, our results support the hypothesis that increased serum IgE levels are associated with age-related cataract.
Recently, age-related cataract has been seen as a multifactorial disease that may be related not only to age and exposure to ultraviolet, but also to systemic conditions [5]. Previous research has revealed that ocular inflammation induced by systemic risk factors—such as smoking, autoimmune diseases, and metabolic disorders—influence cataract formation [31,32]. The major biochemical explanation for this association is that inflammation in the aqueous humor leads to oxidation of the lens proteins [33]. Previous researchers have found that nitric oxide in the aqueous humor, which is induced by several cytokines, may play an important role in the development of age-related cataract [34]. Nitric oxide is a highly reactive molecule that can induce several chemical reactions that denature lens proteins [35]. In addition, one population-based study showed that several systemic inflammatory mediators (high sensitivity C-reactive protein, tumor necrosis factor α, interleukin-6, and intracellular adhesion molecule-1), were associated with age-related cataracts. The authors suggested that nuclear cataracts are related to vascular endothelial dysfunction, which is in turn associated with systemic inflammation, hypertension, and smoking [19]. Interestingly, binding of the mast cell Fc receptor to IgE produces nitric oxide and damages the vascular endothelium [36]. Therefore, these previous investigations may indicate how increased IgE leads to cataract formation.

The possible association between IgE and cataract formation maybe mediated by the mast cell in several ways: the mast cell may aggravate the oxidative status of the lens proteins directly (by activating inflammatory cascades) or indirectly (by increasing vascular permeability). Furthermore, mast cells release several inflammatory mediators, such as cytokines, chemokines, histamine, proteoglycan, and mast cell protease, following IgE stimulation [9]. These mediators are associated with all stages of the inflammatory process, including vasodilation, increase of vascular permeability, and inflammatory cell recruitment [37]. Activation of mast cell induces not only immediate hypersensitivity, but also late responses that cause long-term activation of immune cells; [38] this long-term inflammatory response may aggravate age-related changes such as oxidation of the lens protein. Moreover, a change in vascular permeability may also lead to increased concentrations of oxidative molecules such as nitric oxide in the aqueous humor [39]. These processes have been evidenced by a previous investigation reporting that lens opacity is associated with changes in the components of the aqueous humor [40].

Table 5. The prevalence and odds ratio of cataract in patients with and without an increased total serum IgE level. Data from examined age groups are shown for comparison.

| Age group | Cataract or pseudophakia (%) | No cataract (%) | P-value for χ² test | Adjusted OR of increased total IgE for cataract (95% CI) |
|-----------|-----------------------------|----------------|---------------------|--------------------------------------------------------|
| 40–49 years old | 21 (5.0) 23 (5.5) | 142 (34.1) 230 (55.3) | 0.220 | 1.40 (0.72–2.71) |
| 50–59 years old | 69 (17.7) 64 (16.4) | 128 (32.9) 127 (32.7) | 0.753 | 1.23 (0.76–2.01) |
| ≥60 years old | 143 (39.0) 118 (32.2) | 47 (12.8) 58 (15.8) | 0.083 | 1.54 (0.93–2.53) |

*Adjusted for age, sex, body mass index, smoking, alcohol use, sun exposure, systolic blood pressure, fasting plasma glucose, total cholesterol, asthma, atopic dermatitis, and rheumatoid arthritis.

doi:10.1371/journal.pone.0166331.t005
In the present study, the adjusted multivariable regression models revealed an independent relationship between increased IgE and nuclear cataracts. In our analyses, we adjusted for potential risk factors of age-related cataract; nonetheless, our results may have been influenced by various chronic illnesses associated with both cataract formation and increased IgE level. Recent studies have revealed that IgE-mediated events can lead to several chronic diseases, including not only allergic conditions associated with hypersensitivity, but also metabolic syndrome. In fact, increased serum IgE has been associated with diabetes, hypertension, atherosclerosis, and ischemic heart disease; all these conditions are also related to cataract formation [13]. Furthermore, steroids, which are used to treat IgE-mediated and autoimmune diseases, such as asthma, atopic dermatitis, and rheumatoid arthritis, can also oxidize lens proteins [25]. However, in the current analysis, these conditions were controlled for.

Considering that increased IgE levels were associated with age-related cataracts, it was surprising that IgE sensitization to specific allergens, including Dermatophagoides farinae, cockroach, and dog, showed no significant association. The reason for this finding is unknown. Because sensitization to most of these allergens occurs in childhood, the progression of age-related cataracts in old-aged persons may not be closely associated with the process [27].

According to previous reports, total IgE levels in adults can be influenced by autoimmune disease or lifestyle factors [11]. For example, an association between increased total IgE and smoking has been found in the general population [41]. Additionally, although the mechanism remains unclear, chronic alcohol consumption is also associated with increased total IgE [42]. Overall, total IgE levels may play a role as an inflammatory biomarker that is closely associated with inflammatory responses to non-specific environmental factors, as well as with allergic reactions to specific allergens [13]. Therefore, it stands to reason that increased IgE levels may be associated with age-related cataracts despite the lack of association with IgE sensitization to specific allergens.

This study had certain limitations. Firstly, our analyses did not establish a causal relationship because of their cross-sectional nature. Moreover, our health data was based on a health interview survey taken on one occasion. Fasting plasma glucose, body mass index, blood pressure, and serum IgE may all differ depending on the time of measurement. Secondly, this was a single, Asia-specific study. Generally, the incidence and type of cataract are influenced by genetic background [43]. Therefore, it is uncertain whether our results are relevant to other ethnic groups. Third, slit lamp examinations were performed by many different investigators, and an inter-observer variation could have been introduced, as already discussed in a previous study that used KNHANES data [44]. Despite this limitation, examinations were adequately performed by trained investigators, and risk factors associated with cataract were identified at a nation-wide level. Fourth, dietary intake and nutritional factors were not fully considered in this study. As dietary intake data were collected using an interviewer-administered questionnaire, reporting errors may have occurred because of a recall bias. However, adjustments for plasma glucose, total cholesterol, serum vitamin D concentration, total calorie intake, total vitamin A intake, and total vitamin C intake did not alter our findings (S1 Table). Lastly, we did not consider concomitant corticosteroids, because information about inhaled and oral steroid use was not fully collected as part of the KNHANES 2010. Moreover, the 2010 KNHANES did not collect data regarding several chronic diseases associated with steroid use (e.g., allergic rhinitis [45], inflammatory bowel disease [46], and uveitis [47]); such data could have confounded our findings. In future, it will be necessary to adopt systemic approaches when investigating the long-term effects of drugs associated with cataracts.

In conclusion, our findings demonstrated that increased total IgE levels significantly associated with age-related cataracts. Specifically, increased IgE was significantly related to nuclear cataracts. Due to the aforementioned limitations, further studies involving a larger sample size.
and other ethnicities are still needed. In addition, future studies should clarify more specifically the role of IgE in the development of age-related cataracts.

Supporting Information
S1 Table. Further logistic regression analyses including serum vitamin D, total calorie intake, and total intake of vitamin A and C.

(DOCX)

Acknowledgments
This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: H15C2237).

Author Contributions
Conceptualization: TKY SWK.
Formal analysis: TKY.
Funding acquisition: SWK.
Investigation: SWK KYS.
Methodology: TKY.
Project administration: SWK KYS.
Supervision: SWK KYS.
Writing – original draft: TKY SWK.
Writing – review & editing: SWK KYS.

References
1. Asbell PA, Daulan I, Mindel J, Brocks D, Ahmad M, Epstein S. Age-related cataract. The Lancet. 2005; 365: 599–609. doi: 10.1016/S0140-6736(05)17911-2
2. Li L, Wan X, Zhao G. Meta-analysis of the risk of cataract in type 2 diabetes. BMC Ophthalmol. 2014; 14: 94. doi: 10.1186/1471-2415-14-94 PMID: 25060855
3. Vinson JA. Oxidative stress in cataracts. Pathophysiol Off J Int Soc Pathophysiol ISP. 2006; 13: 151–162. doi: 10.1016/j.pathophys.2006.05.006 PMID: 16765571
4. Beebe DC, Holekamp NM, Shui Y-B. Oxidative damage and the prevention of age-related cataracts. Ophthalmic Res. 2010; 44: 155–165. doi: 10.1159/000316481 PMID: 20829639
5. Park S, Lee E-H. Association between metabolic syndrome and age-related cataract. Int J Ophthalmol. 2015; 8: 804–811. doi: 10.3980/j.issn.2222-3959.2015.04.29 PMID: 26309883
6. Moliazadegan K, Kugelberg M, Lindblad BE, Ludvigsson JF. Increased risk of cataract among 28,000 patients with celiac disease. Am J Epidemiol. 2011; 174: 195–202. doi: 10.1093/aje/kwr069 PMID: 21624959
7. Bae JH, Shin DS, Lee SC, Hwang IC. Sodium Intake and Socioeconomic Status as Risk Factors for Development of Age-Related Cataracts: The Korea National Health and Nutrition Examination Survey. PLOS ONE. 2015; 10: e0136218. doi: 10.1371/journal.pone.0136218 PMID: 26287670
8. Conner ER, Saini SS. The immunoglobulin E receptor: expression and regulation. Curr Allergy Asthma Rep. 2005; 5: 191–196. PMID: 15842956
9. Lippi G, Cervellin G, Sanchis-Gomar F. Immunoglobulin E (IgE) and ischemic heart disease. Which came first, the chicken or the egg? Ann Med. 2014; 46: 456–463. doi: 10.3109/07853890.2014.927714 PMID: 24984051
10. Woodfolk JA, Commins SP, Schuyler AJ, Erwin EA, Platts-Mills TAE. Allergens, sources, particles, and molecules: Why do we make IgE responses? Allergol Int Off J Jpn Soc Allergol. 2015; 64: 295–303. doi: 10.1016/j.alit.2015.06.001 PMID: 26433525

11. Schuenwegh AJM, Ioan-Facsinay A, Dorjée AL, Roos J, Bajema IM, van der Voort EIH, et al. Evidence for a functional role of IgE anticitrullinated protein antibodies in rheumatoid arthritis. Proc Natl Acad Sci. 2010; 107: 2586–2591. doi: 10.1073/pnas.0913054107 PMID: 20133791

12. Bol I, Shi G-P, Kovanen PT. Mast cells as effectors in atherosclerosis. Arterioscler Thromb Vasc Biol. 2015; 35: 265–271. doi: 10.1161/ATVBAHA.114.303570 PMID: 25104798

13. Wang Z, Zhang H, Shen X-H, Jin K-L, Ye G, Qian L, et al. Immunoglobulin E and mast cell proteases are potential risk factors of human pre-diabetes and diabetes mellitus. PLOS ONE. 2011; 6: e28962. doi: 10.1371/journal.pone.0028962 PMID: 22194960

14. Zhang J, Shi G-P. Mast cells and metabolic syndrome. Biochim Biophys Acta. 2012; 1822: 14–20. doi: 10.1016/j.bbadis.2010.12.012 PMID: 21185370

15. Kritas SK, Saggini A, Varvara G, Murmura G, Caraffa A, Antinolfi P, et al. Mast cell involvement in rheumatoid arthritis. J Biol Regul Homeost Agents. 2013; 27: 655–660. PMID: 24152834

16. Theoharides TC, Kalogeromitros D. The critical role of mast cells in allergy and inflammation. Ann N Y Acad Sci. 2006; 1088: 78–99. doi: 10.1196/annals.1366.025 PMID: 17192558

17. Cataracts in atopic dermatitis: a case presentation and review of the literature.—PubMed—NCBI. Available: http://www.ncbi.nlm.nih.gov/pubmed/21242345. Accessed 9 July 2016.

18. Schaumberg DA, Ridker PM, Glynn RJ, Christen WG, Dana MR, Hennekens CH. High levels of plasma C-reactive protein and future risk of age-related cataract. Ann Epidemiol. 1999; 9: 166–171. PMID: 10192648

19. Klein BEK, Klein R, Lee KE, Knudtson MD, Tsai MY. Markers of inflammation, vascular endothelial dysfunction, and age-related cataract. Am J Ophthalmol. 2006; 141: 116–122. doi: 10.1016/j.ajo.2005.08.021 PMID: 16386984

20. Kuang T-M, Tsai S-Y, Hsu W-M, Cheng C-Y, Liu J-H, Chou P. Body mass index and age-related cataract: the Shihpai Eye Study. Arch Ophthalmol Chic Ill 1960. 2005; 123: 1109–1114. doi: 10.1001/archopht.123.8.1109 PMID: 16087846

21. Wu R, Wang J, Mitchell P, et al. Smoking, socioeconomic factors, and age-related cataract: The singapore malay eye study. Arch Ophthalmol. 2010; 128: 1029–1035. doi: 10.1001/archophthalmol.2010.20697004

22. Manson JE, Christen WG, Seddon JM, Glynn RJ, Hennekens CH. A prospective study of alcohol consumption and risk of cataract. Am J Prev Med. 1994; 10: 156–161. PMID: 7917442

23. Taylor HR, West SK, Rosenthal FS, Múñoz B, Newland HS, Abbey H, et al. Effect of ultraviolet radiation on cataract formation. N Engl J Med. 1988; 319: 1429–1433. doi: 10.1056/NEJM198812013192201 PMID: 3185661

24. Klein BE, Klein R, Lee KE. Cardiovascular disease, selected cardiovascular disease risk factors, and age-related cataracts: the Beaver Dam Eye Study. Am J Ophthalmol. 1997; 123: 338–346. PMID: 9063243

25. Jick SS, Vasilakis-Scaramozza C, Maier WC. The risk of cataract among users of inhaled steroids. Epidemiol Camb Mass. 2001; 12: 229–234.

26. Oh K, Lee J, Lee B, Kweon S, Lee Y, Kim Y. Plan and operation of the 4th Korea National Health and Nutrition Examination Survey (KNHANES IV). Korean J Epidemiol. 2007; 29: 139–145.

27. Cheng HM, Kim S, Park G-H, Chang SE, Bang S, Won CH, et al. Low vitamin D levels are associated with atopic dermatitis, but not allergic rhinitis, asthma, or IgE sensitization, in the adult Korean population. J Allergy Clin Immunol. 2014; 133: 1048–1055. doi: 10.1016/j.jaci.2014.01.055 PMID: 24388009

28. Na K-S, Park Y-G, Han K, Mok JW, Joo C-K. Prevalence of and risk factors for age-related and anterior polar cataracts in a Korean population. PLOS ONE. 2014; 9: e96461. doi: 10.1371/journal.pone.0096461 PMID: 24936893

29. Weidinger S, Illig T, Baurecht H, Irvine AD, Rodriguez E, Diaz-Lacava A, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. J Allergy Clin Immunol. 2006; 118: 214–219. doi: 10.1016/j.jaci.2006.05.004 PMID: 16815158

30. Williamson J, Paterson RW, McGavin DD, Jasani MK, Boyle JA, Doig WM. Posterior subcapsular cataracts and glaucoma associated with long-term oral corticosteroid therapy. In patients with rheumatoid arthritis and related conditions. Br J Ophthalmol. 1969; 53: 361–372. PMID: 5794952

31. Shinohara T, Singh DP, Chylack LT. Review: Age-related cataract: immunity and lens epithelium-derived growth factor (LEDGF). J Ocul Pharmacol Ther Off J Assoc Ocul Pharmacol Ther. 2000; 16: 181–191. doi: 10.1089/jop.2000.16.181 PMID: 10803429
32. Alderaan K, Sekicki V, Magder LS, Petri M. Risk factors for cataracts in systemic lupus erythematosus (SLE). Rheumatol Int. 2015; 35: 701–708. doi: 10.1007/s00296-014-3129-5 PMID: 25257763
33. Chen W, Lin H, Zhong X, Liu Z, Geng Y, Xie C, et al. Discrepant expression of cytokines in inflammation- and age-related cataract patients. PLOS ONE. 2014; 9: e109647. doi: 10.1371/journal.pone.0109647 PMID: 25303043
34. Ornek K, Karel F, Büyükböngöl Z. May nitric oxide molecule have a role in the pathogenesis of human cataract? Exp Eye Res. 2003; 76: 23–27. PMID: 12589772
35. Ghahramani M, Yousefi R, Khoshaman K, Alaviamehrz M-M. The impact of calcium ion on structure and aggregation propensity of peroxynitite-modified lens crystallins: new insights into the pathogenesis of cataract disorders. Colloids Surf B Biointerfaces. 2015; 125: 170–180. doi: 10.1016/j.colsurfb.2014.11.002 PMID: 25486325
36. Swindle EJ, Metcalfe DD. The role of reactive oxygen species and nitric oxide in mast cell-dependent inflammatory processes. Immunol Rev. 2007; 217: 186–205. doi: 10.1111/j.1600-065X.2007.00513.x PMID: 17498060
37. Platts-Mills TA. The role of immunoglobulin E in allergy and asthma. Am J Respir Crit Care Med. 2001; 164: S1–5. doi: 10.1164/ajrccm.164.supplement_1.2103024 PMID: 11704610
38. Marshall JS. Mast-cell responses to pathogens. Nat Rev Immunol. 2004; 4: 787–799. doi: 10.1038/nri1460 PMID: 15459670
39. Micera A, Lambiase A, Bonini S. The role of neuromediators in ocular allergy. Curr Opin Allergy Clin Immunol. 2008; 8: 466–471. doi: 10.1097/ACI.0b013e32830e6b17 PMID: 18769203
40. Hayashi T, Era S, Kawai K, Imai H, Nakamura K, Onda E, et al. Observation for redox state of human serum and aqueous humor albumin from patients with senile cataract. Pathophysiology. 2000; 6: 237–243. doi: 10.1016/S0928-4680(99)00022-X
41. Oryszczyn M-P, Annesi-Maesano I, Charpin D, Paty E, Maccario J, Kauffmann F. Relationships of Active and Passive Smoking to Total IgE in Adults of the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA). Am J Respir Crit Care Med. 2000; 161: 1241–1246. doi: 10.1164/ajrccm.161.4.9905027 PMID: 10764318
42. González-Quintela A, Gude F, Boquete O, Rey J, Mejide LM, Suarez F, et al. Association of alcohol consumption with total serum immunoglobulin E levels and allergic sensitization in an adult population-based survey. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2003; 33: 199–205.
43. Pierścionek BK, Weale RA. Odds ratios for different types of age-related cataract: ethnicity and environment. Ophthalmic Res. 1996; 28: 88–92. PMID: 8792358
44. Rim THT, Kim M-H, Kim WC, Kim T-I, Kim EK. Cataract subtype risk factors identified from the Korea National Health and Nutrition Examination survey 2008–2010. BMC Ophthalmol. 2014; 14: 4. doi: 10.1186/1471-2415-14-4 PMID: 24410920
45. Derby L, Maier WC. Risk of cataract among users of intranasal corticosteroids. J Allergy Clin Immunol. 2000; 105: 912–916. doi: 10.1067/mai.2000.106044 PMID: 10808171
46. Mintz R, Feller ER, Bahr RL, Shah SA. Ocular manifestations of inflammatory bowel disease. Inflamm Bowel Dis. 2004; 10: 135–139. PMID: 15168814
47. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI. Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol. 2004; 88: 1159–1162. doi: 10.1136/bjo.2003.037226 PMID: 15317708