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Atopic Dermatitis is Not a Risk Factor for Keratoconus: A Population-based Cohort Study.

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Keratoconus is an eye disorder in which the cornea becomes thin and bulges out in a conical shape. Conflicting results have been reported in literature regarding whether atopic dermatitis (AD) is associated with keratoconus development.^{1,2} So far, only case series have shown an association between AD and keratoconus.³ Hence, we investigated the risk of keratoconus in young Korean patients with AD using the National Health Insurance Service–National Sample Cohort database, which includes a random sample of 1,025,340 Korean, with claims made over a 12-year period (2002–2013).⁴

For analysis 1—a longitudinal cohort analysis—we included 34,375 patients with incident AD (16,159 [47%] women) aged < 20 years who 1) had a disease-free period of at least 2 years before the incident date, and 2) had at least one more AD-related visit and received one of the following drugs within a year of the incident date: oral anti-histamines, topical corticosteroids, or topical calcineurin inhibitors. Among these, we defined patients with severe AD (3,734 cases, 1,571 women [42%]) as those receiving systemic drug(s) for AD treatment in accordance with established guidelines within a year of the incident date.⁵ We matched 4 controls to each AD patient using propensity scores based on age, sex, residential area, and household income; 137,500 controls (11,089 controls for severe cases) were matched for the analysis 1 (Figure 1). There were no significant differences in the incidence probability of newly diagnosed keratoconus between the AD and control groups (0.01% vs. 0.04% at 10 years; $P = 0.16$, Figure 2) and between the severe AD and control groups (0% vs. 0.01% at 10 years; $P = 0.31$). After controlling for age, sex, residential area, household income, and comorbidities, the adjusted hazard ratio of keratoconus was 0.36 (95% CI, 0.08–1.54, $P = 0.17$) in the AD cohort and 1.87 (95% CI, 0.43–8.22, $P = 0.41$) in the severe AD cohort, relative to the control group.

For analysis 2—a nested case-control study—we included 229 patients with incident

keratoconus aged <30 years and 2290 controls matched using propensity scoring as mentioned above. We defined a history of AD as the presence of any AD-related visits within 2 years before the keratoconus incident date, and patient with severe AD as those receiving systemic drugs during these 2 years. There was no significant difference between the keratoconus and control groups in the proportion of patients with AD (7.0% vs. 6.5%; $P = 0.76$) or severe AD (1.8% vs. 1.4%; $P = 0.68$) during the 2 years before the incident date.

We could not define eye rubbing as a control variable in eligible subjects; this is an inherent limitation of studies analyzing claims databases.

In conclusion, our population-based study suggests that AD in young Korean patients is not associated with a risk of keratoconus. However, because of ethnic differences, these findings are not necessarily applicable to other populations. Our results are helpful in that they provide a background for further studies on the association between AD and keratoconus.

75 **ABBREVIATIONS AND ACRONYMS:**

76 **AD**, atopic dermatitis; **AZP**, azathioprine; **CI**, confidence interval; **ICD-10**, international
77 classification of diseases, 10th edition; **INF- γ** , interferon gamma; **IVIG**, intravenous
78 immunoglobulin; **MMF**, mycophenolate mofetil; **MTX**, methotrexate

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Figure legends

Figure 1. Atopic dermatitis. Flow diagram for identifying the incident atopic dermatitis and keratoconus cohorts and their matched controls in Analysis 1 and 2. *AD*, atopic dermatitis; *AZP*, azathioprine; *ICD-10*, international classification of diseases, 10th edition; *INF- γ* , interferon gamma; *IVIG*, intravenous immunoglobulin; *MMF*, mycophenolate mofetil; *MTX*, methotrexate.

Figure 2. Atopic dermatitis. Kaplan–Meier plot of incidence probability of keratoconus in patients with atopic dermatitis and control subjects. There was no statistically significant difference in the incidence probability of keratoconus between the atopic dermatitis and control groups (0.01% and 0.04% at 10 years, respectively; $P = 0.16$, log-rank test).



