JAMA Network Open

Original Investigation | Dermatology

Long-Term Use of Oral Corticosteroids and Safety Outcomes for Patients With Atopic Dermatitis

Yong Hyun Jang, MD, PhD; Eun-Young Choi, PharmD; Hyesung Lee, PhD; Jieun Woo, PharmD; Sohee Park, PharmD, PhD; Yunha Noh, PharmD, PhD; Ja-Young Jeon, PhD; Eun-Young Yoo, MSc; Ju-Young Shin, PhD; Yang Won Lee, MD, PhD

Abstract

IMPORTANCE The use of oral corticosteroids for prolonged periods may be associated with adverse events (AEs). Nevertheless, the risk of AEs with oral corticosteroids, especially among patients with atopic dermatitis (AD), has not been comprehensively investigated and lacks evidence on duration of treatment.

OBJECTIVE To assess the association between long-term exposure to oral corticosteroids and AEs among adult patients with AD.

DESIGN, SETTING, AND PARTICIPANTS This nested case-control study used data from the Health Insurance Review and Assessment Service database of South Korea between January 1, 2012, and October 31, 2021, which included 1 year prior to the cohort entry date of January 1, 2013, for assessing exclusion criteria and baseline characteristics, and 1 year after the study end date of October 31, 2020, to ensure a minimum duration for assessing exposure. Among the population of adults with AD, patients diagnosed with any of 11 AEs were matched with patients who had never received a diagnosis of any of the 11 AEs.

EXPOSURE Long-term use of oral corticosteroids was defined as cumulative supply of more than 30 days or more than 90 days of oral corticosteroid prescription per year.

MAIN OUTCOMES AND MEASURES We used multivariable conditional logistic regression analyses to measure the risk of 11 individual outcomes (osteoporosis, fracture, type 2 diabetes, hyperlipidemia, hypertension, myocardial infarction, stroke, heart failure, avascular necrosis, cataract, or glaucoma) as the composite outcome, controlling for potential confounders. We further classified the composite outcome to individual outcomes to evaluate the AE-specific risk.

RESULTS Among 1 025 270 patients with AD between 2013 and 2020, 164 809 cases (mean [SD] age, 39.4 [14.8]; 56.9% women) were matched with 328 303 controls (mean [SD] age, 39.3 [14.7]; 56.9% women) for sex, age, cohort entry date, follow-up duration, and severity of AD, where the balance of most baseline characteristics was achieved. A total of 5533 cases (3.4%) and 10 561 controls (3.2%) were exposed to oral corticosteroids for more than 30 days, while 684 cases (0.4%) and 1153 controls (0.4%) were exposed to oral corticosteroids for more than 90 days. Overall, there was no increased risk of AEs with use of oral corticosteroids for more than 30 days (adjusted odds ratio [AOR], 1.00; 95% CI, 0.97-1.04), whereas the risk was slightly higher with use of oral corticosteroids for more than 90 days (AOR, 1.11; 95% CI, 1.01-1.23). The small elevation in experiencing an AE was observed with each cumulative or consecutive year of ever long-term use.

(continued)

Key Points

Question What duration of oral corticosteroid use is associated with adverse effects among adult patients with atopic dermatitis?

Findings In this nested case-control study including 1 025 270 patients with atopic dermatitis, use of oral corticosteroids for more than 90 days during 1 year was associated with a slightly increased risk of composite adverse outcomes. There was no increased risk with use of oral corticosteroids for more than 30 days.

Meaning This study suggests that for patients with exacerbations of atopic dermatitis, limiting the duration of oral corticosteroid treatment to 90 days or less may limit adverse effects.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE This case-control study found a slightly increased risk of AEs associated with use of oral corticosteroids for more than 90 days per year, which warrants future research to fully elucidate the observed findings.

JAMA Network Open. 2024;7(7):e2423563. doi:10.1001/jamanetworkopen.2024.23563

Introduction

Atopic dermatitis (AD) is a chronic inflammatory disease that causes serious morbidity, such as pruritus, impaired quality of life, and a range of comorbidities.[1,2] AD is a lifelong condition that relapses chronically and needs constant care.[3] Although AD is considered primarily a pediatric disease, studies have shown high rates of AD among adults as well.[4] The prevalence of AD among adults ranged from 2.1% to 4.9% across countries, and up to 10% of adults required medication for moderate to severe AD due to inadequate response to topical therapies; the prevalence rates were higher among adult patients than among pediatric patients, of whom 1.5% required medication for moderate to severe AD.[5-7]

As AD treatment strategies, international guidelines and expert opinions generally recommend that oral corticosteroids should generally be avoided or limited to the short term only as rescue therapy.[8-11] Nonetheless, given the benefits of oral corticosteroids, including their effectiveness in allergic diseases, short-term safety, and low cost, many patients with moderate to severe AD are treated with oral corticosteroids for prolonged periods, which may constitute inappropriate or excessive use.[12,13] However, oral corticosteroid treatment for prolonged periods could have an association with oral corticosteroid–related complications.[14] Hence, clinical evidence informing patients and practitioners regarding the management of AD exacerbations in routine clinical practice is warranted.

Although previous studies among patients with asthma or rheumatic disease have suggested associations between long-term use of oral corticosteroids and various adverse events (AEs), there are few studies of patients with AD, to our knowledge.[15-21] In addition, existing studies about corticosteroid use among patients with AD were conducted to evaluate the safety concerns primarily about topical corticosteroids.[22-29] Considering the frequent use of oral corticosteroids among adults with AD and the potential association between long-term use of oral corticosteroids and AEs, some of which are severe, there is a need to investigate the safety of the long-term use of oral corticosteroids among adults with AD.[6,30,31] Accordingly, we aimed to investigate the association between long-term use of oral corticosteroids and AEs among adult patients with AD in South Korea.

Methods

Data Source

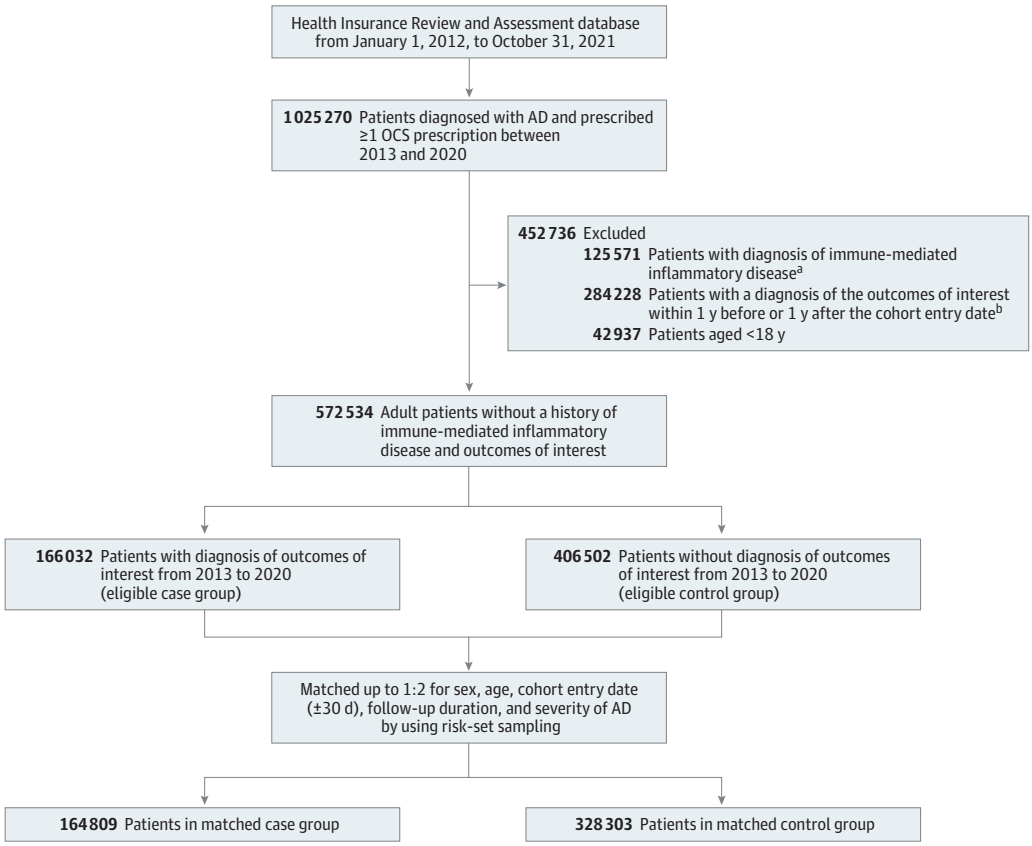
We used the nationwide Health Insurance Review and Assessment Service (HIRA) database of South Korea between January 1, 2012, and October 31, 2021, which included 1 year prior to the cohort entry date of January 1, 2013, for assessing exclusion criteria and baseline characteristics, and 1 year after the study end date of October 31, 2020, to ensure a minimum duration for assessing exposure. It encompasses comprehensive data on health care use for every resident of South Korea, ensuring that patient identifiers are anonymized. The database collects information on socioeconomic and demographic variables, diagnosis (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnostic code; setting of diagnosis; date of diagnosis; and others), and medications prescribed (national drug chemical code, days' supply, dose, date of prescription, route of administration, and others) until the occurrence of emigration or death. A prior validation study examined diagnosis codes documented in the HIRA in comparison with those in electronic

medical records and found an overall positive predictive value of 82.3%.[32] This study was approved by the institutional review board of Sungkyunkwan University, which waived the informed consent because only deidentified data were used in this study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[33]

Study Cohort

The study cohort comprised patients who were prescribed oral corticosteroids at least once with an AD diagnosis code from January 1, 2013, to October 31, 2020. The cohort entry date was defined as the first date of the prescription of oral corticosteroids with an AD diagnosis within the study period to include the new users of oral corticosteroids. Eligible case and control groups were identified after excluding the following: (1) patients with a diagnosis of immune-mediated inflammatory diseases during a 1-year window of exclusion assessment before the cohort entry date, to evaluate the risk of AEs from oral corticosteroid use for AD; (2) patients with a diagnosis of any of 11 outcomes of interest during the exclusion assessment window of 1 year before and 1 year after the cohort entry date, to investigate the association of oral corticosteroid use with newly occurred outcomes; and (3) patients who were younger than 18 years of age on the cohort entry date, to include adult patients (**Figure 1**).

Figure 1. Study Flowchart for the Composite Adverse Outcome



AD indicates atopic dermatitis; OCS, oral corticosteroid.

[a] Rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriasis, Crohn disease, ulcerative colitis, Sjögren syndrome, systemic sclerosis, dermatomyositis, polymyositis, thromboangiitis obliterans, Behçet disease, sarcoidosis, pemphigus, and vitiligo.

[b] Patients who received a diagnosis of the outcomes of interest (osteoporosis, fracture, type 2 diabetes, hyperlipidemia, hypertension, myocardial infarction, stroke, heart failure, avascular necrosis, cataract, or glaucoma) during 1 year before or 1 year after the cohort entry date were excluded.

Case and Control Definition

Cases were defined as patients with AD who received a diagnosis of any of our outcomes of interest after the cohort entry date, and the index date was defined as the first date of outcome occurrence. The composite outcome of interest consisted of osteoporosis, fracture, type 2 diabetes, hyperlipidemia, hypertension, myocardial infarction, stroke, heart failure, avascular necrosis (AVN), cataract, and glaucoma. We defined controls as patients with AD who never received a diagnosis of our outcomes of interests after the cohort entry date. We matched each case with up to 2 controls without replacement, using risk-set sampling on the cohort entry date (±30 days), follow-up duration (between the cohort entry date and the index date [±30 days]), age, sex, and severity of AD. Disease severity of AD was classified as moderate to severe on the basis of the current treatment guidelines for AD.[7] Moderate to severe AD was defined as patients who were receiving at least 1 immunosuppressant, alitretinoin, intravenous immunoglobulin, dupilumab, or phototherapy during the 1 year prior to the cohort entry date. The index dates of the control group were aligned with the corresponding index date of their respective matched cases. For individual outcomes, each case was matched with up to 5 or 10 controls, using different numbers from the composite outcome for ensuring statistical power according to the size of cases for each outcome variable, using risk-set sampling as well (eFigure 2 in Supplement 1).

Exposure

We defined the exposure ascertainment window as the period between the cohort entry date and the index date, segmenting the period into yearly intervals to assess exposure year by year to determine whether patients met the definition for long-term use of oral corticosteroids. Owing to the absence of consensus for a definition of long-term oral corticosteroid use among patients with AD, and even for other diseases, we set the classification of long-term oral corticosteroid use as follows: cumulatively more than 30 days as the primary definition for modest long-term use or more than 90 days as a secondary definition for extensive long-term use, both with greater than a 5-mg daily prednisolone-equivalent dose of oral corticosteroids per year, which places patients at risk of systemic adverse effects.[17] To exclude potential use of oral corticosteroids for related conditions other than AD, we restricted exposure to prescriptions of oral corticosteroids to patients with a diagnosis of AD. *Ever long-term use* was defined as patients with a history of long-term use of oral corticosteroids for at least 1 year, and all remaining patients were defined as *no long-term use*. Primarily, ever long-term use was defined as a binary variable using 2 thresholds (>30 days and >90 days). In addition, to examine the duration-response association with long-term use of oral corticosteroids, we used the year, which met the definition for the long-term use, as a continuous variable. We assessed the risk of each outcome associated with the number of cumulative years (considering all the intermittent years of long-term use of oral corticosteroids) throughout the exposure ascertainment period. We also evaluated the risk associated with the number of consecutive years (considering only the continuous years of long-term use of oral corticosteroids) within the exposure ascertainment period. Details of the exposure assessment are shown in eFigure 3 in Supplement 1.

Covariates

We discerned a sufficient collection of confounding variables that adequately accounted for potential biases in our analysis: demographic characteristics (eg, sex, age, and medical aid recipients), comorbidities (eg, allergic rhinitis, depression, chronic obstructive pulmonary disease, and thyroid disorders), comedications (eg, antidepressants, antibiotics, estrogens, and proton-pump inhibitors), proxies of overall health status (eg, history of hospitalization, number of outpatient visits, and Charlson Comorbidity Index score), and severity of AD. The characteristic assessment window was defined as the 1-year period before the cohort entry date (eFigure 1 in Supplement 1; the demographic characteristics [sex, age, insurance] were assessed on the cohort entry date and other characteristics such as comorbidities, comedications, proxies of health status, and severity of AD

during the 1 year prior to cohort entry). The details of exclusion criteria, exposures, outcomes, and covariates are presented in eTable 2 in Supplement 1.

Statistical Analysis

The demographic characteristics of the cases and controls were presented as frequency (proportion) for categorical variables and as mean (SD) or median (IQR) values for continuous variables. The same analysis used to evaluate the demographic characteristics of the cases and controls of patients with AD were repeated for each of the 11 outcomes as secondary outcomes. Differences in baseline covariates between cases and controls were evaluated using the absolute standardized difference, where an absolute standardized difference greater than 0.1 indicates a statistical imbalance existing between 2 groups.

The association between long-term oral corticosteroid use and the risk of the composite and individual outcomes were investigated using multivariable conditional logistic regression analyses to estimate adjusted odds ratios (AORs) with 95% CIs, adjusting for unbalanced comorbidities, comedications, and proxies of health status after the matching. We conducted additional analyses by considering the number of cumulative or consecutive years of long-term use of oral corticosteroids throughout the entire exposure ascertainment window as continuous variables, to investigate the monotonic duration-response association.

The potential heterogeneity of long-term treatment adverse effects in selected subgroups of patients with AD was examined for the composite adverse outcomes according to age (18-39, 40-64, and ≥65 years), sex (male or female), and severity of AD (mild or moderate to severe AD). To evaluate the robustness of the main findings, sensitivity analyses were first conducted by modifying the definition of exposure from a cumulative duration of more than 30 days or more than 90 days per year to more than 60 days per year. Second, we restricted the population to patients who could be followed up for at least 3 years or 5 years from the cohort entry date. All statistical tests were 2 sided. Analyses were conducted using SAS Enterprise Guide, version 7.1 (SAS Institute Inc), provided by HIRA through a virtual access machine.

Results

Of 1 025 270 patients with AD who had at least 1 prescription of oral corticosteroids between 2013 and 2020, we matched 164 809 cases (mean [SD] age, 39.4 [14.8]; 56.9% women and 43.1% men) with 328 303 controls (mean [SD] age, 39.3 [14.7]; 56.9% women and 43.1% men) (**Table 1**) by 1:2 matching using risk-set sampling. Cases and controls were matched for sex, age, cohort entry date, follow-up duration, and severity of AD; balance was achieved for most covariates between the 2 groups, with an absolute standardized difference of less than 0.1 (Table 1; whole baseline characteristics of cases and controls are presented in eTable 1 in Supplement 1, individual outcomes in eTables 5-15 in Supplement 1, and modest long-term [>30 days] vs extensive long-term [>90 days] in eTable 4 in Supplement 1). The most common comorbidity was allergic rhinitis (cases, 42.2%; controls, 38.7%), and the most prevalently prescribed concurrent medication was antibiotics (cases, 71.3% and controls, 66.8%). All the imbalanced variables of concurrent medication use and number of outpatient visits were additionally adjusted in the multivariable logistic regression.

Among the 164 809 cases and 328 303 controls, 5533 cases (3.4%) and 10 561 controls (3.2%) were exposed to oral corticosteroids over 30 days, and 684 cases (0.4%) and 1153 controls (0.4%) were exposed to oral corticosteroids over 90 days. Overall, the risk of AEs was not associated with use of oral corticosteroids exceeding 30 days (AOR, 1.00; 95% CI, 0.97-1.04) (**Table 2**), while use of oral corticosteroids exceeding 90 days was associated with an 11% increased risk of the composite adverse outcome (AOR, 1.11; 95% CI, 1.01-1.23) (**Table 3**). Each cumulative or consecutive additive year of long-term exposure (>90 days a year) was associated with a slightly increased risk of having an AE (AOR, 1.06; 95% CI, 1.00-1.13 and AOR, 1.06; 95% CI, 1.00-1.13, respectively).

Table 1. Selected Demographic and Clinical Characteristics of Cases and Controls Among Adult Patient (>18 Years) With AD for Composite Outcome

Characteristic	Cases (n = 164 809)	Controls (n = 328 303)	ASD
Age, mean (SD), y	39.4 (14.8)	39.3 (14.7)	0.01
Age, median (IQR), y	38 (26-50)	38 (26-50)	0.01
Age group, No. (%)			
18-39 y	86 761 (52.6)	173 253 (52.8)	0.01
40-64 y	68 901 (41.8)	137 481 (41.9)	
≥65 y	9147 (5.6)	17 569 (5.4)	
Sex, No. (%)			
Male	70 998 (43.1)	141 444 (43.1)	0.00
Female	93 811 (56.9)	186 859 (56.9)	
Medical aid recipients, No. (%)	7588 (4.6)	12 034 (3.7)	0.05
Comorbidities, No. (%)			
Allergic rhinitis	69 480 (42.2)	127 136 (38.7)	0.07
Chronic sinusitis	10 116 (6.1)	17 325 (5.3)	0.04
Conjunctivitis	28 696 (17.4)	50 015 (15.2)	0.06
Anxiety	5713 (3.5)	8633 (2.6)	0.05
Depression	4062 (2.5)	6122 (1.9)	0.04
COPD	17 149 (10.4)	30 037 (9.2)	0.04
Chronic liver disease	3891 (2.4)	5606 (1.7)	0.05
Thyroid disorders	5674 (3.4)	8137 (2.5)	0.06
Comedications, No. (%)			
Antidepressants	9144 (5.6)	14 186 (4.3)	0.06
Antibiotics	117 454 (71.3)	219 356 (66.8)	0.10
Anxiolytics	50 231 (30.5)	88 387 (26.9)	0.08
Azoles	17 581 (10.7)	30 820 (9.4)	0.04
NSAIDs	122 714 (74.5)	228 256 (69.5)	0.11
PPIs	26 930 (16.3)	43 654 (13.3)	0.09
Antihypertensives	7459 (4.5)	11 190 (3.4)	0.06
Lipid-lowering drugs	1222 (0.7)	1467 (0.5)	0.04
Patients hospitalized, No. (%)	15 172 (9.2)	26 028 (7.9)	0.05
No. of outpatient visits, mean (SD)	12.7 (13.7)	10.7 (12.0)	0.15
CCI score, No. (%)			
0	133 052 (80.7)	274 140 (83.5)	0.08
1	11 485 (7.0)	21 251 (6.5)	
2	7853 (4.8)	13 114 (4.0)	
≥3	12 419 (7.5)	19 768 (6.0)	
Moderate to severe AD, No. (%)[a]	1788 (1.1)	2988 (0.9)	0.02
Cohort entry year, No. (%)			
2013	39 376 (23.9)	78 356 (23.9)	0.00
2014	32 380 (19.7)	64 617 (19.7)	
2015	26 705 (16.2)	53 152 (16.2)	
2016	22 989 (14.0)	45 786 (14.0)	
2017	18 805 (11.4)	37 400 (11.4)	
2018	13 308 (8.1)	26 611 (8.1)	
2019	8742 (5.3)	17 408 (5.3)	
2020	2504 (1.5)	4973 (1.5)	
Duration of follow-up, mean (SD), d	1215.1 (657.5)	1215.2 (657.5)	0.00
Duration of follow-up, median (IQR), d	1066 (666-1650)	1066 (666-1650)	0.00

Abbreviations: AD, atopic dermatitis; ASD, absolute standardized difference; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors.

[a] Moderate to severe AD was defined as patients who were receiving at least 1 immunosuppressant, alitretinoin, intravenous immunoglobulin, dupilumab, or phototherapy during the 1 year prior to the cohort entry date.

Table 2. Association Between Long-Term Use of Oral Corticosteroids Among Patients With Atopic Dermatitis and the Risk of Incident Adverse Events for Primary Exposure Definition (>30 d/y)

Outcome	No. (%)		OR (95% CI)	
	Cases	Controls	Crude	Adjusted
Composite outcome (cases, 164 809; controls, 328 303; up to 1:2 risk-set sampling matching)				
Ever long-term use[a]	5533 (3.4)	10 561 (3.2)	1.05 (1.01-1.08)	1.00 (0.97-1.04)
Cumulative No. of years	5533 (3.4)	10 561 (3.2)	1.04 (1.02-1.06)	1.02 (0.99-1.04)
Consecutive No. of years	5533 (3.4)	10 561 (3.2)	1.04 (1.02-1.07)	1.02 (0.99-1.04)
Osteoporosis (cases, 13 673; controls, 129 321; up to 1:10 matching)				
Ever long-term use[a]	359 (2.6)	3186 (2.5)	1.07 (0.96-1.19)	0.97 (0.87-1.09)
Cumulative No. of years	359 (2.6)	3186 (2.5)	1.06 (1.00-1.13)	1.02 (0.96-1.09)
Consecutive No. of years	359 (2.6)	3186 (2.5)	1.07 (0.997-1.14)	1.02 (0.95-1.09)
Fracture (cases, 40 120; controls, 391 118; up to 1:10 matching)				
Ever long-term use[a]	1464 (3.7)	13 324 (3.4)	1.07 (1.02-1.13)	1.02 (0.97-1.08)
Cumulative No. of years	1464 (3.7)	13 324 (3.4)	1.07 (1.04-1.11)	1.05 (1.01-1.08)
Consecutive No. of years	1464 (3.7)	13 324 (3.4)	1.07 (1.04-1.11)	1.05 (1.01-1.08)
Type 2 diabetes (cases, 21 861; controls, 212 807; up to 1:10 matching)				
Ever long-term use[a]	826 (3.8)	7036 (3.3)	1.15 (1.07-1.24)	1.06 (0.98-1.14)
Cumulative No. of years	826 (3.8)	7036 (3.3)	1.08 (1.04-1.12)	1.04 (0.995-1.08)
Consecutive No. of years	826 (3.8)	7036 (3.3)	1.08 (1.04-1.13)	1.04 (0.99-1.09)
Hyperlipidemia (cases, 77 777; controls, 385 023; up to 1:5 matching)				
Ever long-term use[a]	2687 (3.5)	12 312 (3.2)	1.08 (1.04-1.13)	1.02 (0.98-1.07)
Cumulative No. of years	2687 (3.5)	12 312 (3.2)	1.05 (1.03-1.08)	1.02 (0.997-1.05)
Consecutive No. of years	2687 (3.5)	12 312 (3.2)	1.05 (1.03-1.08)	1.02 (0.996-1.05)
Hypertension (cases, 35 179; controls, 338 746; up to 1:10 matching)				
Ever long-term use[a]	1381 (3.9)	11 677 (3.5)	1.14 (1.08-1.21)	1.09 (1.03-1.15)
Cumulative No. of years	1381 (3.9)	11 677 (3.5)	1.08 (1.05-1.12)	1.06 (1.02-1.09)
Consecutive No. of years	1381 (3.9)	11 677 (3.5)	1.08 (1.05-1.12)	1.06 (1.02-1.09)
Myocardial infarction (cases, 769; controls, 7249; up to 1:10 matching)				
Ever long-term use[a]	38 (4.9)	296 (4.1)	1.22 (0.86-1.73)	1.10 (0.77-1.57)
Cumulative No. of years	38 (4.9)	296 (4.1)	1.14 (0.97-1.35)	1.11 (0.93-1.32)
Consecutive No. of years	38 (4.9)	296 (4.1)	1.17 (0.98-1.40)	1.13 (0.94-1.36)
Stroke (cases, 3070; controls, 28 102; up to 1:10 matching)				
Ever long-term use[a]	132 (4.3)	1038 (3.7)	1.17 (0.97-1.41)	1.07 (0.89-1.30)
Cumulative No. of years	132 (4.3)	1038 (3.7)	1.09 (0.98-1.21)	1.05 (0.94-1.17)
Consecutive No. of years	132 (4.3)	1038 (3.7)	1.09 (0.97-1.21)	1.04 (0.93-1.17)
Heart failure (cases, 2858; controls, 26 488; up to 1:10 matching)				
Ever long-term use[a]	114 (4.0)	965 (3.6)	1.10 (0.90-1.34)	0.99 (0.81-1.21)
Cumulative No. of years	114 (4.0)	965 (3.6)	1.04 (0.93-1.17)	0.995 (0.88-1.12)
Consecutive No. of years	114 (4.0)	965 (3.6)	1.06 (0.95-1.20)	1.02 (0.90-1.15)
Avascular necrosis (cases, 602; controls, 5839; up to 1:10 matching)				
Ever long-term use[a]	48 (8.0)	175 (3.0)	2.80 (2.01-3.90)	2.56 (1.82-3.62)
Cumulative No. of years	48 (8.0)	175 (3.0)	1.67 (1.40-1.98)	1.61 (1.35-1.92)
Consecutive No. of years	48 (8.0)	175 (3.0)	1.69 (1.42-2.03)	1.63 (1.36-1.96)
Cataract (cases, 42; controls, 403; up to 1:10 matching)				
Ever long-term use[a]	5 (11.9)	16 (4.0)	3.27 (1.13-9.43)	3.22 (1.05-9.85)
Cumulative No. of years	5 (11.9)	16 (4.0)	1.48 (0.81-2.71)	1.32 (0.71-2.46)
Consecutive No. of years	5 (11.9)	16 (4.0)	1.58 (0.83-2.99)	1.42 (0.72-2.77)
Glaucoma (cases, 45 873; controls, 450 244; up to 1:10 matching)				
Ever long-term use[a]	1575 (3.4)	14 057 (3.1)	1.10 (1.05-1.16)	1.04 (0.98-1.10)
Cumulative No. of years	1575 (3.4)	14 057 (3.1)	1.07 (1.04-1.11)	1.04 (1.01-1.07)
Consecutive No. of years	1575 (3.4)	14 057 (3.1)	1.07 (1.04-1.11)	1.04 (1.00-1.07)

Abbreviation: OR, odds ratio.

[a] The long-term use of oral corticosteroids was defined as a cumulative supply of more than 30 days with a greater than 5-mg daily prednisolone-equivalent dose of oral corticosteroids, which places patients at risk of systemic adverse effects, and we assessed the long-term use of oral corticosteroids annually.

Table 3. Association Between Long-Term Use of Oral Corticosteroids Among Patients With Atopic Dermatitis and the Risk of Incident Adverse Events for Secondary Exposure Definition (>90 d/y)

Outcome	No. (%)		OR (95% CI)	
	Cases	Controls	Crude	Adjusted
Composite outcome (cases, 164 809; controls, 328 303; up to 1:2 risk-set sampling matching)				
Ever long-term use[a]	684 (0.4)	1153 (0.4)	1.18 (1.08-1.30)	1.11 (1.01-1.23)
Cumulative No. of years	684 (0.4)	1153 (0.4)	1.10 (1.03-1.16)	1.06 (1.00-1.13)
Consecutive No. of years	684 (0.4)	1153 (0.4)	1.10 (1.03-1.17)	1.06 (1.00-1.13)
Osteoporosis (cases, 13 673; controls, 129 321; up to 1:10 matching)				
Ever long-term use[a]	40 (0.3)	385 (0.3)	0.98 (0.71-1.36)	0.89 (0.64-1.24)
Cumulative No. of years	40 (0.3)	385 (0.3)	1.01 (0.84-1.22)	0.96 (0.79-1.16)
Consecutive No. of years	40 (0.3)	385 (0.3)	1.00 (0.78-1.20)	0.91 (0.73-1.13)
Fracture (cases, 40 120; controls, 391 118; up to 1:10 matching)				
Ever long-term use[a]	200 (0.5)	1490 (0.4)	1.31 (1.13-1.52)	1.22 (1.05-1.42)
Cumulative No. of years	200 (0.5)	1490 (0.4)	1.18 (1.08-1.29)	1.14 (1.05-1.25)
Consecutive No. of years	200 (0.5)	1490 (0.4)	1.21 (1.10-1.32)	1.17 (1.07-1.29)
Type 2 diabetes (cases, 21 861; controls, 212 807; up to 1:10 matching)				
Ever long-term use[a]	122 (0.6)	937 (0.4)	1.27 (1.05-1.53)	1.13 (0.93-1.37)
Cumulative No. of years	122 (0.6)	937 (0.4)	1.15 (1.04-1.28)	1.10 (0.98-1.23)
Consecutive No. of years	122 (0.6)	937 (0.4)	1.15 (1.03-1.28)	1.09 (0.97-1.22)
Hyperlipidemia (cases, 77 777; controls, 385 023; up to 1:5 matching)				
Ever long-term use[a]	372 (0.5)	1465 (0.4)	1.26 (1.12-1.41)	1.16 (1.03-1.30)
Cumulative No. of years	372 (0.5)	1465 (0.4)	1.11 (1.04-1.19)	1.07 (0.99-1.15)
Consecutive No. of years	372 (0.5)	1465 (0.4)	1.10 (1.03-1.19)	1.06 (0.98-1.14)
Hypertension (cases, 35 179; controls, 338 746; up to 1:10 matching)				
Ever long-term use[a]	200 (0.6)	1593 (0.5)	1.21 (1.04-1.40)	1.13 (0.98-1.31)
Cumulative No. of years	200 (0.6)	1593 (0.5)	1.08 (0.99-1.18)	1.05 (0.96-1.15)
Consecutive No. of years	200 (0.6)	1593 (0.5)	1.09 (0.996-1.19)	1.06 (0.96-1.16)
Myocardial infarction (cases, 769; controls, 7249; up to 1:10 matching)				
Ever long-term use[a]	12 (1.6)	49 (0.7)	2.33 (1.23-4.40)	2.22 (1.17-4.22)
Cumulative No. of years	12 (1.6)	49 (0.7)	1.56 (1.08-2.25)	1.54 (1.06-2.24)
Consecutive No. of years	12 (1.6)	49 (0.7)	1.58 (1.05-2.38)	1.56 (1.03-2.36)
Stroke (cases, 3070; controls, 28 102; up to 1:10 matching)				
Ever long-term use[a]	23 (0.8)	160 (0.6)	1.32 (0.85-2.04)	1.22 (0.78-1.89)
Cumulative No. of years	23 (0.8)	160 (0.6)	1.16 (0.90-1.51)	1.12 (0.85-1.46)
Consecutive No. of years	23 (0.8)	160 (0.6)	1.21 (0.92-1.58)	1.15 (0.87-1.53)
Heart failure (cases, 2858; controls, 26 488; up to 1:10 matching)				
Ever long-term use[a]	16 (0.6)	138 (0.5)	1.08 (0.64-1.81)	0.93 (0.55-1.58)
Cumulative No. of years	16 (0.6)	138 (0.5)	1.02 (0.76-1.37)	0.97 (0.71-1.32)
Consecutive No. of years	16 (0.6)	138 (0.5)	1.04 (0.76-1.42)	0.98 (0.71-1.36)
Avascular necrosis (cases, 602; controls, 5839; up to 1:10 matching)				
Ever long-term use[a]	17 (2.8)	21 (0.4)	8.05 (4.22-15.35)	6.88 (3.53-13.42)
Cumulative No. of years	17 (2.8)	21 (0.4)	2.71 (1.82-4.02)	2.48 (1.68-3.66)
Consecutive No. of years	17 (2.8)	21 (0.4)	2.93 (1.93-4.45)	2.65 (1.76-4.01)
Cataract (cases, 42; controls, 403; up to 1:10 matching)				
Ever long-term use[a]	0	2 (0.5)	NA	NA
Cumulative No. of years	0	2 (0.5)	NA	NA
Consecutive No. of years	0	2 (0.5)	NA	NA
Glaucoma (cases, 45 873; controls, 450 244; up to 1:10 matching)				
Ever long-term use[a]	196 (0.4)	1562 (0.4)	1.23 (1.06-1.43)	1.13 (0.97-1.31)
Cumulative No. of years	196 (0.4)	1562 (0.4)	1.12 (1.03-1.22)	1.08 (0.98-1.18)
Consecutive No. of years	196 (0.4)	1562 (0.4)	1.11 (1.01-1.22)	1.07 (0.97-1.17)

Abbreviations: NA, not applicable; OR, odds ratio.

[a] The long-term use of oral corticosteroids was defined as a cumulative supply of more than 90 days with a greater than 5-mg daily prednisolone-equivalent dose of oral corticosteroids, which places patients at risk of systemic adverse effects, and we assessed the long-term use of oral corticosteroids annually.

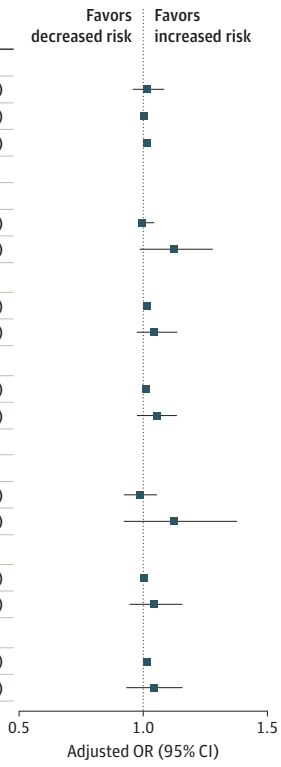
In the analyses of individual outcomes, an increased risk for hypertension (AOR, 1.09; 95% CI, 1.03-1.15), AVN (AOR, 2.56; 95% CI, 1.82-3.62), and cataract (AOR, 3.22; 95% CI, 1.05-9.85) was associated with use of oral corticosteroids for more than 30 days (Table 2). An increased risk for fracture (AOR, 1.22; 95% CI, 1.05-1.42), hyperlipidemia (AOR, 1.16; 95% CI, 1.03-1.30), myocardial infarction (AOR, 2.22; 95% CI, 1.17-4.22), and AVN (AOR, 6.88; 95% CI, 3.53-13.42) was associated with use of oral corticosteroids for more than 90 days (Table 3). In our subgroup analysis, as compared with unexposed patients, the risk of composite AEs associated with long-term use of oral corticosteroids was generally consistent with the main analyses. No differences were observed in the stratified analyses according to the age group, sex, and severity of AD (eFigures 4-6 in Supplement 1). Furthermore, the results of composite outcomes demonstrated a high degree of consistency across all sensitivity analyses regarding the point estimates (**Figure 2**).

Discussion

We identified 164 809 cases and 328 303 controls of comparable patients with AD. The risk of composite adverse outcomes was not associated with with ever long-term use of oral corticosteroids exceeding 30 days, whereas the risk was slightly associated with ever long-term use exceeding 90

Figure 2. Sensitivity Analyses for Evaluating the Risk of the Composite Adverse Outcome Associated With Long-Term Use of Oral Corticosteroids Among Adults With Atopic Dermatitis

Variable	Cases, No. (%)	Controls, No. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Cumulative >60 d/y[a] (cases, 164 809; controls: 328 303)				
Ever long-term use[b]	1640 (1.0)	3045 (0.9)	1.07 (1.01-1.14)	1.02 (0.96-1.09)
Cumulative No. of years	1640 (1.0)	3045 (0.9)	1.04 (1.004-1.08)	1.01 (0.98-1.05)
Consecutive No. of years	1640 (1.0)	3045 (0.9)	1.05 (1.005-1.09)	1.02 (0.98-1.06)
At least 3 y of follow-up[c] (cases, 79 816; controls, 158 999)				
Ever long-term use[b]				
>30 d/y	3078 (3.9)	5893 (3.7)	1.04 (0.997-1.09)	1.00 (0.96-1.05)
>90 d/y	383 (0.5)	643 (0.4)	1.19 (1.05-1.35)	1.13 (0.99-1.28)
Cumulative No. of years				
>30 d/y	3078 (3.9)	5893 (3.7)	1.04 (1.01-1.06)	1.02 (0.99-1.04)
>90 d/y	383 (0.5)	643 (0.4)	1.08 (1.000-1.16)	1.05 (0.98-1.14)
Consecutive No. of years				
>30 d/y	3078 (3.9)	5893 (3.7)	1.04 (1.01-1.07)	1.02 (0.99-1.05)
>90 d/y	383 (0.5)	643 (0.4)	1.08 (0.999-1.16)	1.06 (0.98-1.14)
At least 5 y of follow-up[d] (cases, 32 058; controls, 63 883)				
Ever long-term use[b]				
>30 d/y	1372 (4.3)	2657 (4.2)	1.03 (0.96-1.10)	0.99 (0.93-1.06)
>90 d/y	160 (0.5)	268 (0.4)	1.19 (0.98-1.45)	1.13 (0.93-1.38)
Cumulative No. of years				
>30 d/y	1372 (4.3)	2657 (4.2)	1.03 (0.995-1.06)	1.01 (0.98-1.05)
>90 d/y	160 (0.5)	268 (0.4)	1.07 (0.97-1.18)	1.05 (0.95-1.16)
Consecutive No. of years				
>30 d/y	1372 (4.3)	2657 (4.2)	1.03 (0.995-1.06)	1.02 (0.98-1.06)
>90 d/y	160 (0.5)	268 (0.4)	1.07 (0.96-1.18)	1.05 (0.94-1.16)



OR indicates odds ratio.

[a] Modified definition of the exposure from cumulative duration of more than 30 days per year and more than 90 days per year to a cumulative duration of more than 60 days per year.

[b] The long-term use of oral corticosteroids was defined as a cumulative supply of more than 30 days or more than 90 days with a greater than 5-mg daily prednisolone-equivalent dose of oral corticosteroids, which places patients at risk of systemic adverse effects, and we assessed the long-term use of oral corticosteroids annually. To exclude potential use of oral corticosteroids for conditions other than atopic dermatitis, we restricted exposure to prescriptions for patients with a diagnosis of atopic dermatitis.

[c] Restricted to patients who could be followed up for at least 3 years from the cohort entry date.

[d] Restricted to patients who could be followed up for at least 5 years from the cohort entry date.

days. Also, the cumulative and consecutive years of ever long-term use throughout entire exposure ascertainment period was associated with a monotonic elevated risk of having an AE, although there was not a large discrepancy between the 2 distinctive analyses of additive years. Furthermore, small increased risks were identified in the examination of individual outcomes of fracture, hyperlipidemia, hypertension, myocardial infarction, AVN, and cataract. Generally consistent findings, with regard to point estimates, were observed across a range of sensitivity analyses.

Considering the overlapping pathogenetic mechanism between AD and asthma, we referred to studies of patients with asthma for comparison. One cohort study using Medicaid data found that the use of medium and high doses of systemic corticosteroids was associated with bone, cardiovascular, metabolic, and ocular AEs.[34] Another cohort study using 2000-2014 MarketScan data showed a similar increased risk of various AEs associated with the use of 1 to 3 oral corticosteroid prescriptions (AOR, 1.04; 95% CI, 1.01-1.06) and the use of 4 or more prescriptions (AOR, 1.29; 95% CI, 1.20-1.37); the cumulative burden also increased as the number of years accumulated.[20] Although previous research evaluated the frequency of oral corticosteroid use based on prescription numbers, our study provided more conclusive and valid clinical evidence by defining long-term use based on exact duration.

For individual outcomes, in line with previous studies, we also identified fracture, hypertension, hyperlipidemia, and myocardial infarction as AEs associated with long-term use of oral corticosteroids, owing to interruption of endocrine function and metabolism.[20,35-38] We observed risks of AVN and cataract with long-term oral corticosteroid use, although the risks of these 2 conditions were inconclusive in past studies. For the underlying mechanisms for AVN of the femoral head, the use of oral corticosteroids leads to intravascular coagulation that results in a inhibition of blood flow to the bones, which consequently triggers ischemic injury.[39-41] Although existing evidence regarding an association of AVN with duration of oral corticosteroid treatment is unclear, AVN could be induced from use of just over 30 days, and cumulative exposure is the important determining factor, as shown in our results.[39] Furthermore, although a complete elucidation remains uncertain, the mechanisms of new-onset cataract associated with modest long-term use of oral corticosteroids may be due to disturbances in osmotic equilibrium, oxidative detriment, and perturbations in lens growth factors.[42,43] Another potential hypothesis involves nonenzymatic Schiff base intermediates that form between the corticosteroid's C-20 ketone group and its nucleophilic groups, undergoing Heyns rearrangement to produce stable amine-substituted adducts seen only in corticosteroid-induced posterior subcapsular cataracts.[44,45] No association or subtle increased hazard was observed with osteoporosis, glaucoma, stroke, or heart failure, implying that the dose and duration of corticosteroid treatment may not pose a risk for these conditions among patients with AD.

Strengths and Limitations

This study has some strengths. Concerns about conducting this study arose from the lack of consensus regarding the definition of long-term corticosteroid treatment, as different criteria have been used and variations have been observed (eTable 3 in Supplement 1). Accordingly, we combined the NICE (National Institute for Health and Care Excellence) guidelines[17] with the opinions of clinicians practicing in clinical settings. Even though evidence for a safe continuous duration of corticosteroid treatment was not available as we developed criteria for the definition of long-term treatment for the dichotomous variable, our criteria are expected to serve as a primary threshold for deciding the duration of treatment. In addition, although the long-term use of oral corticosteroids is not recommended in the guideline for treatment of AD, relatively prolonged use of oral corticosteroids is identified frequently in clinical practice.[12] Thus, this study addresses a significant gap in research by investigating the association between long-term oral corticosteroid use and a comprehensive range of AEs specifically among adults with AD. With its substantial sample size, the study provides robust statistical power to detect associations between oral corticosteroid use and relatively rare outcomes, adding to the existing evidence.

This study also has some limitations. First, disparities arose between the diagnoses recorded and the actual diseases a patient had.[46] In addition, HIRA data do not include clinical data; accordingly, the diagnostic standard criteria for AD, such as the Hanifin-Rajka criteria,[47,48] were infeasible. To comply with this issue, we included patients with AD who had at least 1 oral corticosteroid prescription and restricted prescriptions to patients with a diagnosis of AD. Second, due to the inbuilt characteristics of database recording drugs that are prescribed rather than drugs that are taken, the exposure measurement could be uncertain. However, we set the exposed group from the modest long term (>30 days) to the extensive long term (>90 days) and also included the numbers of cumulative or consecutive years of ever long-term use, from which the cumulative burden would be appropriately measured. Third, inhaled corticosteroids, which have some degree of systemic bioavailability, and topical and eye drop formulations of corticosteroids were not accounted for in this study. Fourth, for some of the individual study outcomes, we could not rule out the failure to detect the true effect due to the lack of statistical power; thus, future studies are warranted to corroborate these results. Fifth, due to the nature of the case-control design, it is not possible to completely exclude reverse causality. Sixth, although we considered moderate to severe AD using prescriptions of medication based on the treatment guideline, the influence of AD-related disease severity cannot be eliminated. Seventh, we addressed residual or unmeasured confounders by calculating E-values (eTables 16 and 17 in Supplement 1), but unmeasured confounders may be present, and the results should be interpreted with caution.

Conclusions

In this large population-based case-control study, we discovered that oral corticosteroid use of more than 90 days among individuals with AD was associated with a small increased risk of composite adverse outcomes. Future investigations are warranted to confirm this potential risk of AEs associated with long-term use of oral corticosteroids for patients with exacerbations of AD, and health care professionals should thoroughly weigh the benefits associated with oral corticosteroids against the observed small risk of AEs, while continuously monitoring for AEs.

ARTICLE INFORMATION

Accepted for Publication: May 23, 2024.

Published: July 19, 2024. doi:10.1001/jamanetworkopen.2024.23563

Corresponding Authors: Ju-Young Shin, PhD, School of Pharmacy, Sungkyunkwan University, 2066 Saburo, Jangan-gu, Suwon, Gyeonggi-do 16419, South Korea (shin.jy@skku.edu); Yang Won Lee, MD, PhD, Department of Dermatology, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, South Korea (20050078@kuh.ac.kr).

Author Affiliations: Department of Dermatology, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Korea (Jang); School of Pharmacy, Sungkyunkwan University, Suwon, South Korea (Choi, H. Lee, Park, Noh, Shin); Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon, South Korea (H. Lee, Woo, Shin); Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom (Park); School of Pharmacy, Aston University, Birmingham, United Kingdom (Park); Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada (Noh); Department of Inflammation & Immunology Medical Affairs, Pfizer Pharmaceuticals Korea Ltd, Seoul, South Korea (Jeon, Yoo); Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, South Korea (Shin); Department of Dermatology, Konkuk University School of Medicine, Seoul, South Korea (Y. W. Lee).

Author Contributions: Drs Shin and Y. W. Lee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Jang and Choi contributed equally to this work.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: H. Lee, Noh, Jeon, Yoo.

Drafting of the manuscript: Jang, Choi, Woo, Jeon, Yoo.

Critical review of the manuscript for important intellectual content: Jang, H. Lee, Woo, Park, Noh, Jeon, Yoo, Shin, Y. W. Lee.

Statistical analysis: Choi, H. Lee, Woo, Park.

Obtained funding: Jeon, Yoo, Shin.

Administrative, technical, or material support: Jeon, Yoo, Shin, Y. W. Lee.

Supervision: Jang, Shin.

Conflict of Interest Disclosures: Dr Park reported receiving support from the AIR@innoHK programme of the Government of Hong Kong Special Administrative Region Innovation and Technology Commission. Dr Noh reported receiving grants from the Ministry of Health and Welfare outside the submitted work. Drs Jeon and Yoo reported receiving personal fees from Pfizer Pharmaceuticals Korea Ltd outside the submitted work. Dr Shin reported receiving grants from the Ministry of Food and Drug Safety, the Ministry of Health and Welfare, the National Research Foundation of Korea, Celltrion, and SK Bioscience outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported by Pfizer Pharmaceuticals Korea Ltd.

Role of the Funder/Sponsor: Pfizer Pharmaceuticals Korea Ltd had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol*. 2017;137(1):26-30. doi:10.1016/j.jid.2016.07.012

2. Davis DMR, Drucker AM, Alikhan A, et al. American Academy of Dermatology guidelines: awareness of comorbidities associated with atopic dermatitis in adults. *J Am Acad Dermatol*. 2022;86(6):1335-1336. doi:10.1016/j.jaad.2022.01.009

3. Williams HC. Clinical practice: atopic dermatitis. *N Engl J Med*. 2005;352(22):2314-2324. doi:10.1056/NEJMcp042803

4. Sacotte R, Silverberg JI. Epidemiology of adult atopic dermatitis. *Clin Dermatol*. 2018;36(5):595-605. doi:10.1016/j.clindermatol.2018.05.007

5. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy*. 2018;73(6):1284-1293. doi:10.1111/all.13401

6. Lee JH, Choi A, Noh Y, et al. Real-world treatment patterns for atopic dermatitis in South Korea. *Sci Rep*. 2022;12(1):13626. doi:10.1038/s41598-022-17222-y

7. Lynde CW, Bourcier M, Gooderham M, et al. A treatment algorithm for moderate to severe atopic dermatitis in adults. *J Cutan Med Surg*. 2018;22(1):78-83. doi:10.1177/1203475417733460

8. Arkwright PD, Motala C, Subramanian H, Spergel J, Schneider LC, Wollenberg A; Atopic Dermatitis Working Group of the Allergic Skin Diseases Committee of the AAAAI. Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract*. 2013;1(2):142-151. doi:10.1016/j.jaip.2012.09.002

9. Drucker AM, Eyerich K, de Bruin-Weller MS, et al. Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. *Br J Dermatol*. 2018;178(3):768-775. doi:10.1111/bjd.15928

10. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on atopic eczema, part I: systemic therapy. *J Eur Acad Dermatol Venereol*. 2022;36(9):1409-1431. doi:10.1111/jdv.18345

11. Davis DMR, Drucker AM, Alikhan A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. *J Am Acad Dermatol*. 2024;90(2):e43-e56. doi:10.1016/j.jaad.2023.08.102

12. Lee JH, Kim JE, Park GH, et al. Consensus update for systemic treatment of atopic dermatitis. *Ann Dermatol*. 2021;33(6):497-514. doi:10.5021/ad.2021.33.6.497

13. Carbone A, Siu A, Patel R. Pediatric atopic dermatitis: a review of the medical management. *Ann Pharmacother*. 2010;44(9):1448-1458. doi:10.1345/aph.1P098

14. Yu SH, Drucker AM, Lebwohl M, Silverberg JI. A systematic review of the safety and efficacy of systemic corticosteroids in atopic dermatitis. *J Am Acad Dermatol*. 2018;78(4):733-740.e11. doi:10.1016/j.jaad.2017.09.074

15. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med*. 1994;96(2):115-123. doi:10.1016/0002-9343(94)90131-7

16. Majumdar SR, Morin SN, Lix LM, Leslie WD. Influence of recency and duration of glucocorticoid use on bone mineral density and risk of fractures: population-based cohort study. *Osteoporos Int*. 2013;24(9):2493-2498. doi:10.1007/s00198-013-2352-3

17. Mundell L, Lindemann R, Douglas J. Monitoring long-term oral corticosteroids. *BMJ Open Qual*. 2017;6(2):e000209. doi:10.1136/bmjoq-2017-000209

18. Dalal AA, Duh MS, Gozalo L, et al. Dose-response relationship between long-term systemic corticosteroid use and related complications in patients with severe asthma. *J Manag Care Spec Pharm*. 2016;22(7):833-847. doi:10.18553/jmcp.2016.22.7.833

19. Zazzali JL, Broder MS, Omachi TA, Chang E, Sun GH, Raimundo K. Risk of corticosteroid-related adverse events in asthma patients with high oral corticosteroid use. *Allergy Asthma Proc*. 2015;36(4):268-274. doi:10.2500/aap.2015.36.3863

20. Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol*. 2018;141(1):110-116. doi:10.1016/j.jaci.2017.04.009

21. Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Tran TN. Burden of chronic oral corticosteroid use by adults with persistent asthma. *J Allergy Clin Immunol Pract*. 2017;5(4):1050-1060. doi:10.1016/j.jaip.2016.12.023

22. Glazenburg EJ, Wolkerstorfer A, Gerretsen AL, Mulder PG, Oranje AP. Efficacy and safety of fluticasone propionate 0.005% ointment in the long-term maintenance treatment of children with atopic dermatitis: differences between boys and girls? *Pediatr Allergy Immunol*. 2009;20(1):59-66. doi:10.1111/j.1399-3038.2008.00735.x

23. Schmitt J, von Kobyletzki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol*. 2011;164(2):415-428. doi:10.1111/j.1365-2133.2010.10030.x

24. Mukovozov IM, Morra DE, Giustini D, Tadrous M, Cheung AM, Drucker AM. Atopic dermatitis and bone health: a systematic review. *J Eur Acad Dermatol Venereol*. 2021;35(3):615-628. doi:10.1111/jdv.16895

25. Tasker F, Brown A, Grindlay DJC, Rogers NK, Harman KE. What's new in atopic eczema? an analysis of systematic reviews published in 2018, part 1: prevention and topical therapies. *Clin Exp Dermatol*. 2020;45(8):974-979. doi:10.1111/ced.14303

26. Davallow Ghajar L, Wood Heickman LK, Conaway M, Rogol AD. Low risk of adrenal insufficiency after use of low- to moderate-potency topical corticosteroids for children with atopic dermatitis. *Clin Pediatr (Phila)*. 2019;58(4):406-412. doi:10.1177/0009922818825154

27. Wood Heickman LK, Davallow Ghajar L, Conaway M, Rogol AD. Evaluation of hypothalamic-pituitary-adrenal axis suppression following cutaneous use of topical corticosteroids in children: a meta-analysis. *Horm Res Paediatr*. 2018;89(6):389-396. doi:10.1159/000489125

28. Ratib S, Burden-Teh E, Leonardi-Bee J, Harwood C, Bath-Hextall F. Long-term topical corticosteroid use and risk of skin cancer: a systematic review. *JBI Database System Rev Implement Rep*. 2018;16(6):1387-1397. doi:10.11124/JBISRIR-2017-003393

29. Callen J, Chamlin S, Eichenfield LF, et al. A systematic review of the safety of topical therapies for atopic dermatitis. *Br J Dermatol*. 2007;156(2):203-221. doi:10.1111/j.1365-2133.2006.07538.x

30. Mora T, Sánchez-Collado I, Mullol J, Muñoz-Cano R, Ribó P, Valero A. Prevalence of atopic dermatitis in the adult population of Catalonia (Spain): a retrospective, large-scale population-based study. *J Investig Allergol Clin Immunol*. 2023;0:0.

31. Eckert L, Amand C, Gadkari A, Rout R, Hudson R, Ardern-Jones M. Treatment patterns in UK adult patients with atopic dermatitis treated with systemic immunosuppressants: data from The Health Improvement Network (THIN). *J Dermatolog Treat*. 2020;31(8):815-820. doi:10.1080/09546634.2019.1639604

32. Park BJ, Sung SJ, Park KD, Seo SW, Kim SW. Report of the evaluation for validity of discharged diagnoses in Korean Health Insurance database. ScienceOpen.com. 2003. Accessed May 28, 2023. https://www.scienceopen.com/document?vid=fdacfead-9b03-4426-a8cb-349e463b8aff

33. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573-577. doi:10.7326/0003-4819-147-8-200710160-00010

34. Lefebvre P, Duh MS, Lafeuille MH, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol*. 2015;136(6):1488-1495. doi:10.1016/j.jaci.2015.07.046

35. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res*. 2000;15(6):993-1000. doi:10.1359/jbmr.2000.15.6.993

36. Mebrahtu TF, Morgan AW, West RM, Stewart PM, Pujades-Rodriguez M. Oral glucocorticoids and incidence of hypertension in people with chronic inflammatory diseases: a population-based cohort study. *CMAJ*. 2020;192(12):E295-E301. doi:10.1503/cmaj.191012

37. Atik N, Hayati RU, Hamijoyo L. Correlation between steroid therapy and lipid profile in systemic lupus erythematosus patients. *Open Access Rheumatol*. 2020;12:41-46. doi:10.2147/OARRR.S245662

38. Varas-Lorenzo C, Rodriguez LA, Maguire A, Castellsague J, Perez-Gutthann S. Use of oral corticosteroids and the risk of acute myocardial infarction. *Atherosclerosis*. 2007;192(2):376-383. doi:10.1016/j.atherosclerosis.2006.05.019

39. Chan KL, Mok CC. Glucocorticoid-induced avascular bone necrosis: diagnosis and management. *Open Orthop J*. 2012;6:449-457. doi:10.2174/1874325001206010449

40. Jones JP Jr. Fat embolism and osteonecrosis. *Orthop Clin North Am*. 1985;16(4):595-633. doi:10.1016/S0030-5898(20)30431-4

41. Cui Q, Wang GJ, Balian G. Steroid-induced adipogenesis in a pluripotential cell line from bone marrow. *J Bone Joint Surg Am*. 1997;79(7):1054-1063. doi:10.2106/00004623-199707000-00012

42. Jobling AI, Augusteyn RC. What causes steroid cataracts? a review of steroid-induced posterior subcapsular cataracts. *Clin Exp Optom*. 2002;85(2):61-75. doi:10.1111/j.1444-0938.2002.tb03011.x

43. James ER. The etiology of steroid cataract. *J Ocul Pharmacol Ther*. 2007;23(5):403-420. doi:10.1089/jop.2006.0067

44. Manabe S, Bucala R, Cerami A. Nonenzymatic addition of glucocorticoids to lens proteins in steroid-induced cataracts. *J Clin Invest*. 1984;74(5):1803-1810. doi:10.1172/JCI111599

45. Comstock TL, Decory HH. Advances in corticosteroid therapy for ocular inflammation: loteprednol etabonate. *Int J Inflam*. 2012;2012:789623. doi:10.1155/2012/789623

46. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci*. 2017;32(5):718-728. doi:10.3346/jkms.2017.32.5.718

47. Rudzki E, Samochocki Z, Rebandel P, et al. Frequency and significance of the major and minor features of Hanifin and Rajka among patients with atopic dermatitis. *Dermatology*. 1994;189(1):41-46. doi:10.1159/000246781

48. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338-351. doi:10.1016/j.jaad.2013.10.010

SUPPLEMENT 1.

eTable 1. Demographic and Clinical Characteristics of Cases and Controls of Adult Patients (>18 Years) With Atopic Dermatitis for Composite Outcome
eTable 2. Codes Used to Define Exclusion Criteria, Exposures, Outcomes, and Covariates
eTable 3. Exposure Definition Regarding to Long-Term Oral Corticosteroid Usage in the Previous Studies
eTable 4. Demographic and Clinical Characteristics of Cases and Controls of Adult Patients (>18 Years) With Atopic Dermatitis, Comparison Between Ever Long-Term Use of OCS Over 30 Days vs 90 Days
eTable 5. Demographic and Clinical Characteristics of Cases and Controls of Adult Patients (>18 Years) With Atopic Dermatitis: Osteoporosis
eTable 6. Demographic and Clinical Characteristics of Cases and Controls of Adult Patients (>18 Years) With Atopic Dermatitis: Fracture
eTable 7. Demographic and Clinical Characteristics of Cases and Controls of Adult Patients (>18 Years) With Atopic Dermatitis: Type 2 Diabetes Mellitus
eTable 8. Demographic and Clinical Characteristics of Cases and Controls of Adult Patients (>18 Years) With Atopic Dermatitis: Hyperlipidemia