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Fracture risks in patients with atopic dermatitis

A nationwide matched cohort study

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ABSTRACT

Background: The risk of osteoporosis has been explored in atopic dermatitis (AD). The long-term risk of fractures in patients with AD and the effects of various AD treatments on bone health remain to be elucidated.
Objective: To evaluate the long-term risk of fractures in patients with AD.
Methods: This nationwide matched cohort study was conducted using the National Health Insurance Research Database of Taiwan for the period 1997 to 2013. A total of 36,855 patients with AD and 147,420 reference subjects without AD were identified. Demographic characteristics and comorbidities were compared, and cumulative incidence of fractures was evaluated. Adjusted hazard ratios for fracture risks of AD and various AD treatments were calculated using the Cox proportional hazards model.
Results: A total of 1518 patients (4.12%) in the AD cohort and 5579 patients (3.78%) in the reference cohort had fractures ($P = .003$). The mean ages were 22.6 years in both groups. The 16-year cumulative incidence of fractures in the AD cohort (8.043%) was significantly higher than that in the reference cohort (7.366%) ($P = .002$). Severe AD (adjusted hazard ratio [aHR], 1.31; 95% confidence interval [CI], 1.08-1.59) was independently associated with fractures. Other independent risk factors included exposure to topical (aHR, 1.21; 95% CI, 1.05-1.39) or systemic (≥10 mg/d; aHR, 1.62; 95% CI, 1.38-1.91) corticosteroids. Use of disease-modifying antirheumatic drugs (aHR, 0.71; 95% CI, 0.53-0.90) and phototherapy (aHR, 0.73; 95% CI, 0.56-0.95) was associated with a lower risk of fractures. The results were consistent across sensitivity analyses.
Conclusion: Patients with AD have a higher incidence of fractures. Severe AD is independently associated with fractures.

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease worldwide.[1,2] In addition to cutaneous eruption and other atopic conditions, AD is associated with substantial comorbidities, including immunologic, cardiometabolic, and psychiatric diseases.[1] Chronic inflammation has been proposed as the underlying link between AD and these morbidities.[3]

Recent studies have suggested that chronic inflammation in AD is detrimental to bone health.[4] Patients with AD have been found to have reduced bone mineral density (BMD) and increased risk of osteoporosis compared with controls.[5,6] From the result of cross-sectional studies[7] and 1 cohort study,[8] eczema or AD is strongly associated with fractures in both children and adults. Nevertheless, there is inconsistency across the literature,[9,10] and the existing research is scarce and mainly of cross-sectional design with limited information on fracture sites, exposure to corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and phototherapy, and other potential confounders. Because AD is prevalent and fracture is associated with high morbidity, mortality, and economic burden,[11] risk assessment of fracture in patients with AD is of great importance.

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The aim of this study is to investigate the long-term risk and risk factors of fractures in patients with AD.

Methods

Study Design

This nationwide cohort study included patients with the diagnosis of AD and matched control subjects from the Longitudinal Health Insurance Database (LHID) 2000 and LHID 2010, subsets of the National Health Insurance Research Database (NHIRD) of Taiwan, for the period 1997 to 2013. The NHIRD has been validated[12] and used extensively in epidemiologic studies in Taiwan.[13-15] The LHID 2000 and LHID 2010 contain the most updated data since 1997 of the randomly sampled 1,000,000 individuals from the NHIRD in 2000 and 2010, respectively. There is no important difference in the age and sex distribution or average insured payroll-related amount between the subjects in the LHIDs and the original NHIRD. In the databases, the diagnostic codes are in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) with diagnoses made by board-certified physicians in the corresponding specialties. Personal information including body weight, height, family history, laboratory examination results, lifestyle, and habits such as smoking and alcohol use is not available from the NHIRD.

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan (No. 2017-08-005CC).

Participants and Matched Controls

All patients with a primary diagnosis of AD (ICD-9-CM code 691.8) for the first time between 1997 and 2013 were eligible for inclusion in this study. We enrolled subjects who had received a major diagnosis of AD more than 3 times in an outpatient department or who had been admitted to a hospital for AD by a dermatologist, immunologist, or rheumatologist. Reference subjects without a history of AD were randomly selected from LHID 2000 and LHID 2010. All sampled individuals were followed up until the end of 2013, outcome of interest, registration of death, or withdrawal from the National Health Insurance program of Taiwan.

Index date was defined as the date of first AD diagnosis or the corresponding date for non-AD reference subjects. As a history of fracture confers an increased risk of future fractures,[16] subjects with fracture before the index date were excluded.

We matched each subject in the AD group with 4 reference subjects without AD by age, sex, index date, and propensity score. The propensity score, which was based on acute coronary syndrome, hypertension, diabetes mellitus, hyperthyroidism, asthma, chronic liver disease, and autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus, and Sjogren's syndrome, was calculated using logistic regression model.[17] Finally, a total of 36,855 patients with AD and 147,420 matched reference subjects were enrolled.

Reliability of the retrieved information was independently verified by 2 statisticians.

Outcome Measurement

The disease of outcome included fracture at any site (ICD-9 codes 733.1, V13.51, 805, 806, 808, 812.0-812.5, 813, 820, 821.0-821.3, 823, 824) for which there was hospital admission or the same diagnosis at least 3 times. Fractures were categorized as pathologic fractures (ICD-9 codes 733.1, V13.51) or fractures of the vertebral column (ICD-9 codes 805, 806), pelvis (ICD-9 code 808), humerus (ICD-9 codes 812.0-812.5), radius and ulna (ICD-9 code 813), femur neck (ICD-9 code 820), femur (ICD-9 codes 821.0-821.3), tibia and fibula (ICD-9 code 823), or ankle (ICD-9 code 824).

Covariate Factors

Demographic factors, such as age, sex, number of hospital visits, disease duration, and comorbidities directly related to fractures such as osteoporosis and postmenopausal status, were considered potential confounders. Other comorbidities that indirectly confound the chances for fracture based on the effects of competing risk of mortality were identified, including acute coronary syndrome, hypertension, hyperlipidemia, diabetes mellitus, hyperthyroidism, asthma, chronic liver disease, autoimmune diseases, psoriasis, cerebral vascular accident, epilepsy, and cancer. Comorbid diseases were included if diagnosed at least 3 times or in the inpatient data sets at least once before the index date. Patients with RA, systemic lupus erythematosus, Sjogren's syndrome, or malignancy were identified from the Registry for Catastrophic Illness Patient Database, a separate subpart of the NHIRD. Insured patients who have a major disease, such as malignancy, can apply for a catastrophic illness certificate, which grants exemption from all copayments. Applications for catastrophic illness certificates are validated by at least 2 specialists based on careful examination of medical records, laboratory data, and imaging studies, as described previously.[13,18]

Topical corticosteroids and systemic medications frequently prescribed for AD, such as corticosteroids, DMARDs including methotrexate, cyclosporine, and azathioprine, and phototherapy including psoralen and ultraviolet A and ultraviolet B, were also analyzed. Medication use was defined as administration for more than 30 days per year of observation time.

Statistical Analysis

The demographic data of the study population were first analyzed. We compared the demographic factors and prevalence rates of disease of outcome between the 2 study cohorts by χ^2 test. The cumulative incidences of fractures at all sites were compared between the AD cohort and the reference cohort using log-rank test. To account for heterogeneity of the study subjects owing to unmeasured covariates, we performed multivariate analyses of the matched study groups under the proportional hazards model to evaluate the independent risk factors for fractures at all sites.

Furthermore, we conducted sensitivity analysis to ensure consistent results across different subgroups of patients, by restricting the study subjects to patients with moderate-to-severe AD. Patients with moderate-to-severe AD were defined as those who had been admitted for AD or with exposure to phototherapy, systemic corticosteroids (≥10 mg/d), or DMARDs for at least 30 days per year during follow-up.

Data were managed with SAS 9.4 software (SAS Institute Inc, Cary, North Carolina). Calculations of cumulative incidences and Cox models were carried out with the "cmprsk" package of R (http://cran.r-project.org/web/packages/cmprsk/index.html). Calculated results are expressed as the estimated number together with 95% confidence interval (CI).

Results

Demographic Characteristics and Cumulative Incidences of Fractures in Study Cohorts

The subjects in both study cohorts were selected according to the process presented in eFigure 1. Demographic characteristics and associated comorbidities are illustrated in Table 1. The mean age in both groups of patients was 22.6 years. The mean follow-up time was 6.8 years in both cohorts. The patients with AD had more

Table 1
Demographic Characteristics of Matched Study Patients in Both Cohorts

Characteristics	AD, N=36,855 (%)	Reference, N=147,420 (%)	*P* value
Age, y			
Mean ± SD	22.6 ± 21.0	22.6 ± 20.9	.93
Median (Q1-Q3)	15.3 (5.2-36.0)	15.4 (5.2-35.9)	.78
Hospital visit, N			
Mean ± SD	149.0 ± 144.8	108.9 ± 112.7	<.001
Median (Q1-Q3)	112.0 (53.0-199.0)	78.0 (33.0-148.0)	<.001
Ever admitted for AD	787 (2.14)	0	—
Follow-up, y			
Mean ± SD	6.8 ± 4.0	6.8 ± 3.9	.53
Median (Q1-Q3)	6.6 (3.4-9.9)	6.6 (3.4-9.8)	.59
Female	19,144 (51.94)	76,576 (51.94)	>.99
Male	17,711 (48.06)	70,844 (48.06)	
Comorbidities			
Acute coronary syndrome	1254 (3.40)	4951 (3.36)	.68
Hypertension	2683 (7.28)	10,562 (7.16)	.45
Hyperlipidemia	1014 (2.75)	3936 (2.67)	.39
Diabetes mellitus	1256 (3.41)	4930 (3.34)	.55
Hyperthyroidism	85 (0.23)	272 (0.18)	.08
Asthma	5984 (16.24)	21,555 (14.62)	<.001
Chronic liver disease	2345 (6.36)	8900 (6.04)	.02
Autoimmune disease	211 (0.57)	705 (0.48)	.02
Rheumatoid arthritis	70 (0.19)	313 (0.21)	.43
Systemic lupus erythematosus	100 (0.27)	269 (0.18)	<.001
Sjogren's syndrome	45 (0.12)	170 (0.12)	.79
Psoriasis	247 (0.67)	725 (0.49)	<.001
Osteoporosis	565 (1.53)	2068 (1.40)	.06
Postmenopause	977 (2.65)	3771 (2.56)	.32
Cerebral vascular accident	757 (2.05)	2913 (1.98)	.34
Epilepsy	286 (0.78)	1178 (0.80)	.67
Cancer	318 (0.86)	1279 (0.87)	.95
Medication use			
Topical steroids	2052 (5.6)	1469 (1.0)	<.001
Systemic steroids	1002 (2.7)	1301 (0.9)	<.001
DMARDs	496 (1.3)	866 (0.6)	<.001
Phototherapy	680 (1.8%)	515 (0.3%)	<.001
PUVA	82 (0.2%)	87 (0.1%)	<.001
UVB	598 (1.6%)	428 (0.3%)	<.001
Phototherapy times, median (Q1-Q3)	18.0 (6.0-54.0)	18.0 (6.0-66.0)	.92
PUVA times, median (Q1-Q3)	18.0 (6.0-49.2)	18.0 (6.0-42.0)	.66
UVB times, median (Q1-Q3)	18.0 (6.0-48.0)	18.0 (6.0-67.2)	.38

Abbreviations: AD, atopic dermatitis; DMARDs, disease-modifying antirheumatic drugs; N, number; PUVA, psoralen and ultraviolet A; Q, quartile; UVB, ultraviolet B.

comorbidities than non-AD reference subjects, including asthma, chronic liver disease, autoimmune disease, and psoriasis. Exposure to topical and systemic corticosteroids, DMARDs, and phototherapy was also more common among patients with AD (Table 1).

A total of 1518 patients (4.12%) in the AD cohort and 5579 patients (3.78%) in the reference cohort had fractures when all sites were considered ($P = .003$) (Table 2). Among them, vertebral fractures (0.65%) were more common in patients with AD than in reference subjects (0.52%). This difference was statistically significant ($P = .004$). The detailed number of patients who have been diagnosed of having fracture or lost to follow-up for every plural years is presented in eTable 1 and eTable 2.

The 16-year cumulative incidence of fractures in the AD cohort (8.043%) was significantly higher than that in the reference cohort (7.366%) ($P = .002$) (Fig 1). The cumulative incidence of fracture further increased in those with moderate-to-severe AD (10.669%) ($P < .001$) (Fig 2).

Multivariate Analyses for Risk Factors of Fractures

We next conducted univariate and multivariate analyses to identify the predicting factors for fractures. Increasing age, hospital visits, male sex, comorbidities, and exposure to topical and systemic corticosteroids, DMARDs, and phototherapy were identified on univariate analysis (eTable 3).

Table 2
Prevalence of Fractures of Matched Study Patients in Both Cohorts

Characteristics	AD, N=36,855 (%)	Reference, N=147,420 (%)	*P* value
Fracture, all sites	1518 (4.12)	5579 (3.78)	.003
Pathologic fracture	91 (0.25)	292 (0.20)	.07
Vertebral fracture	238 (0.65)	766 (0.52)	.004
Pelvis	45 (0.12)	134 (0.09)	.10
Humerus	217 (0.59)	843 (0.57)	.72
Radius and ulna	619 (1.68)	2363 (1.60)	.30
Femur neck	115 (0.31)	451 (0.31)	.89
Femur, other	75 (0.20)	282 (0.19)	.68
Tibia and fibula	200 (0.54)	715 (0.49)	.17
Ankle	137 (0.37)	495 (0.34)	.31

Abbreviations: AD, atopic dermatitis; N, number.

Results of multivariate analysis revealed that moderate-to-severe AD (adjusted hazard ratio [aHR], 1.31; 95% CI, 1.08-1.59; $P = .006$) was independently associated with fractures, after adjusting for confounders (Table 3). Other independent risk factors included osteoporosis (aHR, 1.63; 95% CI, 1.45-1.82), exposure to systemic corticosteroids greater than or equal to 10 mg/d (aHR, 1.62; 95% CI, 1.38-1.91) or topical corticosteroids (aHR, 1.21; 95% CI, 1.05-1.39), male sex (aHR, 1.51; 95% CI, 1.44-1.59), postmenopausal status (aHR, 1.18; 95% CI, 1.06-1.32), and each incremental year of age (aHR, 1.01; 95% CI, 1.01-1.01). Use of DMARDs (aHR, 0.71; 95% CI, 0.53-0.90; $P = .01$) and phototherapy (aHR, 0.73; 95% CI, 0.56-0.95; $P = .02$) was associated with a lower risk of fractures (Table 3). These results were consistent across sensitivity analyses (Table 4).

Discussion

The results of this nationwide cohort study suggest that AD is associated with fractures, especially in severe AD (aHR, 1.31; 95% CI, 1.08-1.59; $P = .006$). The negative effects of AD on bone heath are independent of exposure to topical or systemic corticosteroids. There is particularly strong evidence for the association between AD and fractures of the vertebrae, which are the most common osteoporotic fractures.[19,20]

Chronic inflammation might be the main cause of poor bone health and fractures in people with AD. Under physiological conditions, the activities of osteoclasts and osteoblasts are coupled for skeletal homeostasis. In inflammatory situations, proinflammatory molecules, including interleukin (IL)-1, IL-6, IL-17, IL-31, IL-33, tumor necrosis factor α, and receptor activator of nuclear factor κB ligand, stimulate osteoclast precursors and accelerate bone resorption.[4,21-23] Animal studies have revealed decreased blood flow in the bone marrow.[24] Increased levels of the aforementioned cytokines have also been found in a mouse model of dermatitis.[24] Hence, IL-17, IL-31, IL-33, and tumor necrosis factor α have been proposed to be costimulators of AD and osteoclastogenesis.[25]

Other factors related to low BMD in people with AD include obesity,[26] dietary restrictions for atopic diathesis resulting in deficiencies in vitamin D, calcium, and essential nutritents,[5,27,28] and genetics. There may be shared genetic mutation, such as ZDHHC13, or single-nucleotide polymorphism, such as rs479844, near the AP5B1 gene.[29-31] This genetic pleiotropy might be responsible for the shared biological pathways between these 2 seemingly unrelated phenotypes.

Corticosteroid use is another strong risk factor for fractures. A previous case-control study has addressed no increase in fracture risk associated with corticosteroids in dermal preparation.[32] Nevertheless, the short observation period of only 4 years and lack of exposure-time analyses in the research limit interpretation of the study results. Recently, a nationwide retrospective cohort study over 15-

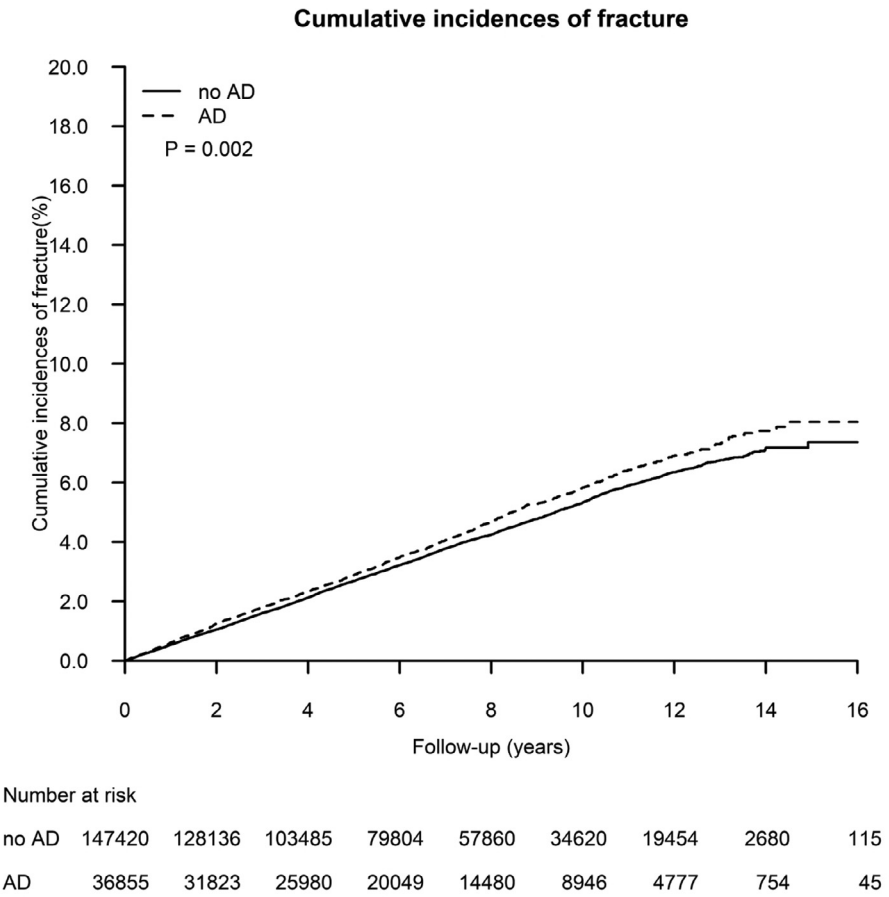

Figure 1. Cumulative incidences of fracture in patients with AD and matched controls. The differences between the 2 study cohorts were calculated by log-rank test. AD, atopic dermatitis.

year period revealed that use of potent topical corticosteroids increased the risk of osteoporosis and fractures with a dose-response association for cumulative use.[33] This finding implies that, even though the bioavailability is less than 1% for cutaneously administered corticosteroids,[34] the prolonged use of topical corticosteroids as the first-line anti-inflammatory treatment or maintenance therapy for AD[35,36] may still cause a large cumulative absorption of corticosteroids in systemic circulation and detrimental effects on bone health.

Evidence has suggested that systemic corticosteroid taken at a high dose for a long duration results in increased risk of fractures.[37] Although not recommended for long-term therapy for AD in clinical guidelines, systemic corticosteroids are administered to individuals with acute flare-ups or as a bridging therapy.[38] Among patients with AD, the suggested dosage of oral corticosteroids is up to 0.5 mg/kg/d. Nevertheless, evidence of the optimal duration of systemic corticosteroids is still lacking.[38,39] In the present study, use of topical corticosteroids (aHR, 1.21; 95% CI, 1.05-1.39; P = .009) or systemic prednisolone of more than 10 mg/d (aHR, 1.62; 95% CI, 1.38-1.91; P < .001) for longer than 3 months was an independent risk factor for fractures. This suggests that caution is warranted in the use of both topical and systemic corticosteroids to prevent patients with AD from experiencing further bone loss.

There is a conflicting association between fractures and DMARDs which are frequently used in AD. Previous studies have reported that methotrexate may increase the risks of bone loss and fractures in patients with osteosarcoma or leukemia.[40,41] Nevertheless, no adverse effect of methotrexate on bone formation in RA was found.[42,43] Cyclosporine inhibits osteoclastogenesis in vitro[44] but enhances bone resorption in vivo.[45] Treatment with cyclosporine may lead to a decrease in BMD but is not associated with an increase in risk of fracture.[46] Azathioprine is bone sparing in rats[47] but associated with an increased risk of fracture in humans.[48] Phototherapy, however, was found to have positive effects on bone mineralization. Studies have revealed patients receiving phototherapy to have elevated serum vitamin D levels,[49] increased BMD,[50] and decreased risk of fractures.[51] The underlying mechanism may relate to the induction of vitamin D synthesis by ultraviolet. In the present study, use of DMARDs (aHR, 0.71; 95% CI, 0.53-0.90; P = .01) or phototherapy (aHR, 0.73; 95% CI, 0.56-0.95; P = .02) was negatively associated with fracture. The influence of phototherapy on osteohomeostasis was in line with the previous studies. The anti-inflammatory effects of DMARDs seem to outweigh their osteoporotic potential. Nevertheless, these findings are limited to those with more severe AD, because exposure to DMARDs in the present study was defined as average exposure time during the observation period. A new study design is needed to investigate the protective effects of DMARDs in patients with AD.

In general, female sex is a risk factor for osteoporosis and fracture.[11] Nevertheless, the present study revealed that male sex is associated with a higher fracture risk in AD (aHR, 1.51; 95% CI, 1.44-1.59). This association might be explained by the younger AD population. Younger male individuals often exhibit high levels of physical activity. Moreover, premenopausal females have lower rates of bone turnover. Other independent risk factors such as each incremental year of age (aHR, 1.01; 95% CI, 1.01-1.01), postmenopausal status (aHR, 1.18; 95% CI, 1.06-1.32), and osteoporosis (aHR, 1.63; 95% CI, 1.45-1.82) also support this viewpoint.

The strength of this study is its population-based cohort study design. The prospective registration of fractures enables us to evaluate the temporal relationship, which differs from cross-sectional studies.[7] The effects of various AD treatments on bone health, which

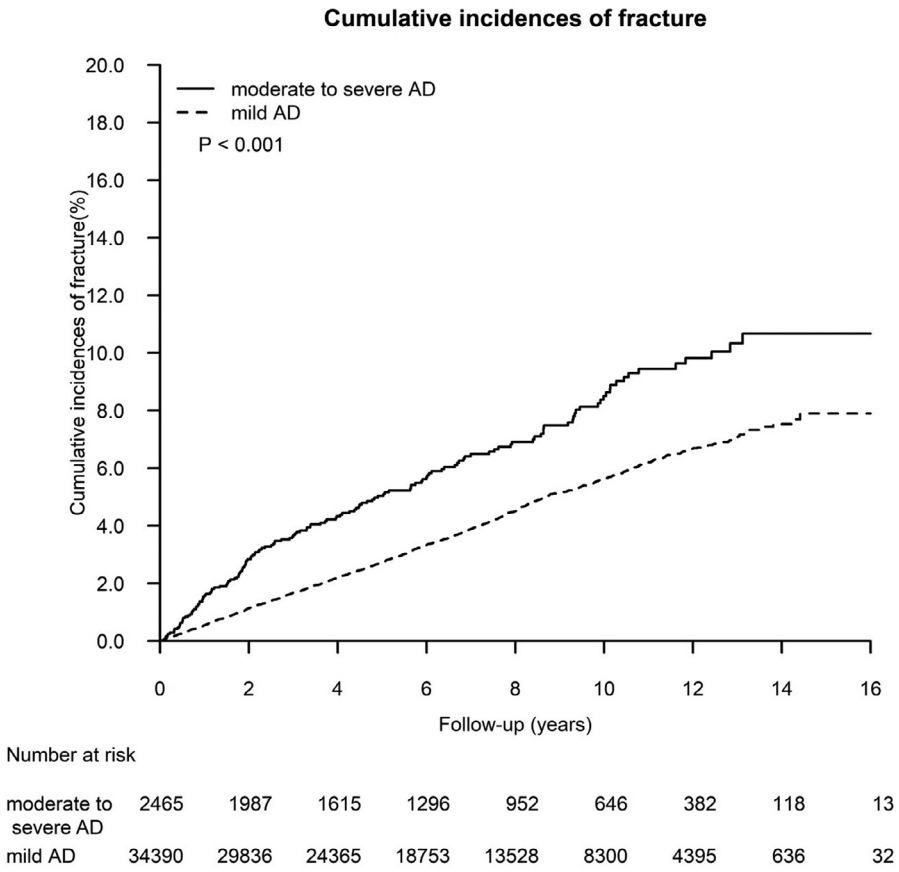

Figure 2. Cumulative incidences of fracture in patients with moderate-to-severe AD and matched controls. The differences between the 2 cohorts were calculated by log-rank test. AD, atopic dermatitis.

Table 3
Multivariate Analysis of Predicting Factors for Fractures Among Study Subjects

Characteristics	Adjusted hazard ratio[a] (95% CI)	*P* value
Each incremental year of age	1.01 (1.01-1.01)	<.001
Male	1.51 (1.44-1.59)	<.001
Hospital visiting times	1.00 (1.00-1.00)	<.001
Atopic dermatitis	1.03 (0.97-1.09)	.35
Moderate-to-severe atopic dermatitis[b]	1.31 (1.08-1.59)	.006
Rheumatoid arthritis	1.09 (0.78-1.53)	.61
Osteoporosis	1.63 (1.45-1.82)	<.001
Postmenopause	1.18 (1.06-1.32)	.003
Topical corticosteroids	1.21 (1.05-1.39)	.009
Systemic corticosteroids	1.62 (1.38-1.91)	<.001
DMARDs	0.71 (0.53-0.90)	.01
Phototherapy	0.73 (0.56-0.95)	.02

Abbreviations: CI, confidence interval; DMARDs, disease-modifying antirheumatic drugs.
[a]Hazard ratios were adjusted for all variables listed in the table.
[b]After substitution of moderate-to-severe atopic dermatitis for atopic dermatitis in the same model on the multivariate analysis.

are lacking in the literature, were evaluated, and the robustness of our findings was confirmed on sensitivity analysis.

There are some limitations to the present study. First, as this was an observational study, we were unable to infer causality. We can only report an association between increased fracture risk and AD. Second, information regarding several confounding factors associated with increased fracture risk is unavailable from the NHIRD, including level of physical activity,[52] body mass index,[27] diet,[5,27,28] smoking habit,[52] alcohol consumption,[53] laboratory examination or patch test results, and use of biologics (not be reimbursed before 2013 in Taiwan). To minimize biases, we selected study subjects for the 2 cohorts by matching age, sex, index dates, and propensity score and performed multivariable analyses to adjust for potential confounders. Third, the potency and the exposure of body surface area of topical corticosteroids are difficult to estimate in the current study. In addition, patient adherence and skin integrity information that are unavailable from the NHIRD can affect systemic absorption of topical corticosteroids. We, therefore, conducted multivariate analysis, and AD was found to be an independent risk factor for fractures. This

Table 4
Sensitivity Analysis for the Association Between Atopic Dermatitis and Fractures

	Adjusted hazard ratio (95% CI)		
Characteristics	Model 1[a]	Model 2[b]	Model 3[c]
Atopic dermatitis	1.07 (1.01-1.13)	1.05 (0.99-1.11)	1.01 (0.95-1.08)
Moderate-to-severe atopic dermatitis	1.56 (1.31-1.86)	1.41 (1.18-1.68)	1.29 (1.06-1.58)

Abbreviation: CI, confidence interval.
[a]Adjusted for all statistically significant variables but topical corticosteroids and phototherapy listed in eTable 1.
[b]Adjusted for factors in model 1 plus topical corticosteroids.
[c]Adjusted for factors in model 2 plus phototherapy.

result was consistent across sensitivity analyses regardless of consideration of topical corticosteroids. To evaluate the effects of topical corticosteroids on bone health of patients with AD, additional research is necessary. Fourth, misclassification bias might exist owing to coding errors. Hence, we selected subjects with AD and fractures coded in outpatient data sets at least 3 times or in inpatient data sets at least once. Finally, similar to other epidemiologic studies, the present study may suffer from surveillance bias as populations with AD are more likely to consult physicians and to have fracture data recorded. Nevertheless, owing to the National Health Insurance program in Taiwan, there is fair accessibility to medical treatment and low out-of-pocket payment. Therefore, most Taiwanese seek medical care on feeling discomfort. This unique health care-seeking behavior helps guard against the possibility of surveillance bias.

In conclusion, the results of this nationwide matched cohort study revealed an increased risk of fractures in patients with AD. Severe AD and exposure to both topical and systemic corticosteroids were independently associated with fractures. Use of DMARDs or phototherapy was associated with a lower risk of fractures. It is necessary to raise awareness of the risk of fractures among people with AD.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2021.09.004.

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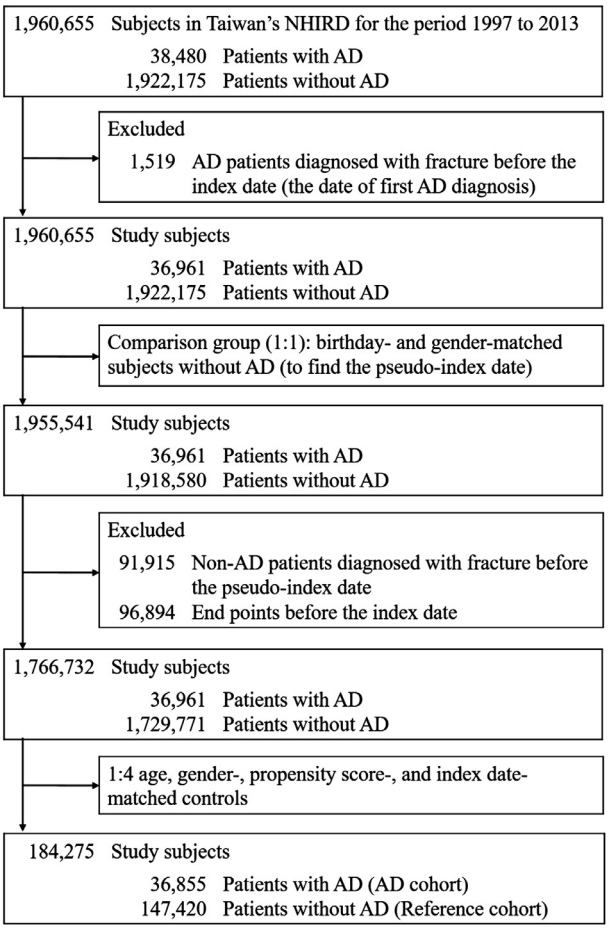
Supplementary data



eFigure 1. Selection process for subjects in both study cohorts. AD, atopic dermatitis; NHIRD, National Health Insurance Research Database.

eTable 1
The Number of Patients With AD and Reference Patients Who Reached the Study End Points for Every Plural Years

Study subjects	Follow-up period, y	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16
Patients with AD	Reaching study end points	5032	5843	5931	5569	5534	4169	4023	709
	Fracture	432	322	278	219	154	83	28	2
	Death	254	263	243	204	196	168	127	22
	LTFU for other reasons[a]	4346	5258	5410	5146	5184	3918	3868	685
Reference patients	Reaching study end points	19,284	24,651	23,681	21,944	23,240	15,166	16,774	2565
	Fracture	1476	1276	1062	777	564	323	100	1
	Death	1459	1389	1294	1152	1012	727	590	77
	LTFU for other reasons[a]	16,349	21,986	21,325	20,015	21,664	14,116	16,084	2487

Abbreviations: AD, atopic dermatitis; LTFU, loss to follow-up.
[a]The reasons of withdrawal from the National Health Insurance program of Taiwan are unavailable in the databases.

eTable 2
The Number of Patients With Mild and Moderate-to-Severe AD Who Reach the Study End Points for Every Plural Years

Study subjects	Follow-up period, y	0-2	2-4	4-6	6-8	8-10	10-12	12-14	14-16
Patients with mild AD	Reaching study end points	4554	5471	5612	5225	5228	3905	3759	604
	Fracture	368	293	256	203	139	74	25	2
	Death	198	225	214	170	179	152	117	18
	LTFU for other reasons[a]	3988	4953	5142	4852	4910	3679	3617	584
Patients with moderate-to-severe AD	Reaching study end points	478	372	319	344	306	264	264	105
	Fracture	64	29	22	16	15	9	3	0
	Death	56	38	29	34	17	16	10	4
	LTFU for other reasons[a]	358	305	268	294	274	239	251	101

Abbreviations: AD, atopic dermatitis; LTFU, loss to follow-up.
[a]The reasons of withdrawal from the National Health Insurance program of Taiwan are unavailable in the databases.

eTable 3
Univariate Analysis of Predicting Factors for Fractures Among Study Subjects

Characteristics	Number	Fracture	Hazard ratio (95% CI)	*P* value
Age	—	—	1.02 (1.02-1.02)	<.001
Hospital visits number	—	—	1.00 (1.00-1.00)	<.001
Male	88,555	4035	1.38 (1.32-1.45)	<.001
AD	36,855	1518	1.09 (1.03-1.16)	.002
Moderate-to-severe AD[a]	2465	158	1.68 (1.43-1.97)	<.001
Acute coronary syndrome	9931	858	2.46 (2.29-2.64)	<.001
Hypertension	20,672	1580	2.31 (2.18-2.44)	<.001
Hyperlipidemia	9554	513	1.47 (1.23-1.73)	<.001
Diabetes mellitus	10,650	740	1.90 (1.76-2.05)	<.001
Hyperthyroidism	1000	37	0.95 (0.69-1.31)	.75
Asthma	41,614	1817	1.13 (1.07-1.19)	<.001
Chronic liver disease	17,314	842	1.33 (1.24-1.43)	<.001
Autoimmune disease	1445	75	1.41 (1.13-1.78)	.003
Rheumatoid arthritis	562	39	1.95 (1.43-2.68)	<.001
Systemic lupus erythematosus	485	22	1.20 (0.79-1.83)	.39
Sjogren's syndrome	461	21	1.24 (0.80-1.90)	.33
Psoriasis	1542	70	1.27 (1.00-1.60)	.049
Osteoporosis	3822	488	3.63 (3.31-3.98)	<.001
Postmenopause	6878	505	2.03 (1.86-2.23)	<.001
Cerebral vascular accident	6536	619	2.60 (2.39-2.82)	<.001
Epilepsy	2165	130	1.46 (1.23-1.73)	<.001
Cancer	3616	177	1.21 (1.04-1.40)	.01
Topical corticosteroids	3521	299	2.80 (2.449-3.15)	<.001
Systemic corticosteroids	2303	215	2.85 (2.48-3.26)	<.001
DMARDs	1362	67	1.40 (1.10-1.78)	.006
Phototherapy	1195	67	1.35 (1.06-1.71)	.01

Abbreviations: AD, atopic dermatitis; CI, confidence interval; DMARD, disease-modifying antirheumatic drug.
[a]Refer to patients with AD admitted to hospital for AD or who received phototherapy, systemic corticosteroids (≥10 mg/d), or DMARDs for more than 30 days per year during the observation period.