

# Fracture incidence in children after developing atopic dermatitis: A Korean nationwide birth cohort study

**Running head:** Atopic dermatitis and fracture in children

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### **Authors contribution**

Dr DKY and DIS had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. *Study concept and design:* SWL, YHS, JIS, DKY, and DIS; *Acquisition, analysis, or interpretation of data:* SWL, YHS, JIS, DKY, and DIS; *Drafting of the manuscript:* SWL, YHS, JIS, DKY, and DIS; *Critical revision of the manuscript for important intellectual content:* all authors; *Statistical analysis:* SWL, YHS, JIS, DKY, and DIS; *Study supervision:* SWL, DKY, and DIS. DKY is guarantor for this study. The corresponding author attests that

81 all listed authors meet authorship criteria and that no others meeting the criteria have been  
82 omitted.

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## To the Editor

Previous studies have determined the relationship between atopic dermatitis (AD) and the risk of fractures.<sup>1-3</sup> However, there may be inconclusive due to inappropriate study design, existing recall bias, inadequate adjustment for confounders, small sample size, short-term follow-up period, and inclusion of adult participants only.<sup>1-3</sup> This large-scale, population-based, nationwide birth cohort study investigated the relationship between AD diagnosis and fracture incidence in 1.78 million children in South Korea.

The study analyzed a dataset from the National Health Insurance Service in South Korea<sup>4</sup> on Korean children born between January 1, 2009, and December 31, 2015, and included in the first National Health Screening Program for Infants and Children. The sample size was 1,778,588 infants. The study protocol was approved by the Institutional Review Board of Sejong University (Seoul, South Korea; SJU-HR-E-2021-001) and Seoul National University (Seoul, South Korea; E-2108-134-1246). The need for written informed consent was waived because of the use of routinely collected health data.

AD was defined using the ICD-10 code (L20; AD) with at least two claims within 1 year and at least two records for AD therapy (topical and systemic corticosteroids, calcineurin inhibitors, and systemic immunosuppressants [azathioprine, cyclosporine, mycophenolate mofetil, and methotrexate])<sup>3</sup>. By default, all children were classified as having mild AD unless they were treated with the immunosuppressants mentioned above while presenting moderate to severe AD<sup>3</sup>.

The primary outcome was the first diagnosis of fracture based on the appropriate ICD-10 code<sup>5,6</sup>. Secondary outcomes were fractures in different anatomical sites, including the head, spine, upper limb, lower limb, and other sites due to the frequency of fracture in children.<sup>5</sup>

The follow-up ended on December 31, 2019, at death, or at the first diagnosis of fracture. The fracture incidence rate is expressed per 1,000 person-years. We generated 1:3 exposure-driven propensity score-matched cohorts to determine the robustness and generalization of the main findings and to reduce immortal time bias. The effect of AD on the risk of fractures was assessed using a Cox proportional hazards regression model with hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA), R software version 3.1.1 (R Foundation, Vienna, Austria), and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).<sup>7</sup> A p-value of less than 0.05 was considered statistically significant.

The demographic and clinical characteristics of our cohort (858,246 females [48.3%] and 920,342 males [51.8%]) are shown in Table S1. During the follow-up period (mean duration, 7.52 years; total person-years, 13,378,356), 342,601 children (19.3%) were diagnosed with AD. In the matched cohort, children with AD had a 14% greater likelihood of developing fractures than controls (33.37 vs. 28.88 per 1,000 person-years) after adjusting for confounders (Table 1). The risk of fracture increased with AD severity (28.88, 33.08, and 35.54 per 1,000 person-years in the control, mild AD, and moderate to severe AD groups. The risk of fracture increased by 12% in children with mild AD (adjusted HR [aHR], 1.12; 95% CI, 1.11–1.14) and 23% in those with moderate to severe AD (aHR, 1.23; 95% CI, 1.20–1.26). To reduce the risk of detection bias or reverse causation, we performed an additional analysis to determine whether age at diagnosis influenced fracture risk. We found that early onset increased fracture risk (aHR for first diagnosis at age <2 years, 1.19 [95% CI: 1.18–1.21]; aHR for first diagnosis at age 2–4 years, 1.08 [95% CI: 1.06–1.10]; and aHR for first diagnosis at age ≥5 years, 1.03 [95% CI: 1.01–1.06]).

The excess risk for overall fracture following AD diagnosis was greater at 0–1 year of age after AD diagnosis (aHR, 1.53; 95% CI: 1.49–1.57), and this risk persisted until 5 years of age (Figure 1). The risk of fracture at different sites following AD development is presented in Table S2. The effect size was similar across fracture sites: head (aHR, 1.13; 95% CI: 1.10–1.15); spine (aHR, 1.33; 95% CI: 1.13–1.58); upper limb (aHR, 1.06; 95% CI: 1.05–1.07); lower limb (aHR, 1.13; 95% CI: 1.12–1.15); and other sites (aHR, 1.21; 95% CI: 1.14–1.23). In addition, fracture risk was similar according to sex, birth year, birth season, region of residence, and history of breastfeeding (Table S3). An additional analysis of the null hypothesis indicated that the incident rate of thyroid disorders and chronic kidney disease was not associated with AD (null hypothesis; Table S4).

Several factors may underlie the association of AD with fracture risk in children, including the interaction between immune and bone cells, dietary habits, calcium and vitamin D intake, physical activity, psychological and behavioral disorders, sleep quality, and the effect of systemic corticosteroids on bone mineral metabolism.<sup>8</sup>

Our study has limitations. First, although we used a large sample size of 1.78 million children, children who did not participate in the national health examination survey were excluded from the analysis. Second, potential confounding factors or mediators (vitamin D level, malnourishment, sleep quality, psychological status, and physical activity) were not considered because claims-based data were not collected systematically. Therefore, confounding and selection bias may limit data interpretation. Third, AD diagnosis was established based on ICD-10 codes, which may be inaccurate; however, previous studies validated electronic health record data using similar methods. A recent questionnaire-based definition of AD indicated a prevalence of 10%–20%, and our definition of AD (19.3%) was



reliable.<sup>1-3,8</sup>

In this nationally representative cohort study, we observed that AD development was associated with an increased risk of subsequent fracture, and this risk was pronounced according to the severity of AD. Additionally, the earlier onset age of AD had a higher risk of fracture. Moreover, the risk for fracture was greatest during 0–1 year of age following the first diagnosis of AD, and an increased risk persisted for up to 5 years of age after the first diagnosis of AD.

**Word count: 932**

#### **Declaration of interests**

Dr Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). That study has received funding from Janssen corporation. The other authors declare no competing interests.

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200 atopic dermatitis. *The Journal of allergy and clinical immunology*. 2020;145(2):487-  
201 488.

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204 Table 1. Cox proportional hazards model to determine the relationship of atopic dermatitis with subsequent overall bone fracture in full  
205 unmatched cohort (n=1,778,588) and 1:3 propensity score-matched cohort (n=1,370,404)

					Hazard ratio (95% CI)		
Parameter	N (%)	Fracture events	Person-years	Fracture incidence rate*	Crude	Model 1 <sup>§</sup>	Model 2 <sup>‡</sup>
Full unmatched cohort (n=1,778,588)							
<b>Atopic dermatitis</b>							
None	1,435,987	239,300	10,778,966	22.20	1.0 (reference)	1.0 (reference)	1.0 (reference)
Atopic dermatitis	342,601	65,429	2,599,390	25.17	<b>1.12 (1.11 to 1.13)</b>	<b>1.12 (1.11 to 1.13)</b>	<b>1.09 (1.08 to 1.10)</b>
Severity of atopic dermatitis							
None	1,435,987	239,300	10,778,966	22.20	1.0 (reference)	1.0 (reference)	1.0 (reference)
Mild atopic dermatitis	298,737	54,337	2,274,308	23.89	<b>1.12 (1.11 to 1.13)</b>	<b>1.11 (1.10 to 1.12)</b>	<b>1.09 (1.08 to 1.10)</b>
Moderate to severe atopic dermatitis	43,864	8092	325,081	24.89	<b>1.13 (1.11 to 1.16)</b>	<b>1.13 (1.11 to 1.16)</b>	<b>1.11 (1.08 to 1.13)</b>

1:3 propensity score-matched cohort (n=1,370,404)							
<b>Atopic dermatitis</b>							
None	1,027,803	169,954	5,884,387	28.88	1.0 (reference)	1.0 (reference)	1.0 (reference)
Atopic dermatitis	342,601	65,429	1,960,856	33.37	<b>1.16 (1.15 to 1.17)</b>	<b>1.16 (1.15 to 1.17)</b>	<b>1.14 (1.13 to 1.15)</b>
Severity of atopic dermatitis							
None	1,027,803	169,954	5,884,387	28.88	1.0 (reference)	1.0 (reference)	1.0 (reference)
Mild atopic dermatitis	298,737	57,337	1,733,197	33.08	<b>1.15 (1.14 to 1.16)</b>	<b>1.15 (1.14 to 1.16)</b>	<b>1.12 (1.11 to 1.14)</b>
Moderate to severe atopic dermatitis	43,864	8092	227,659	35.54	<b>1.25 (1.22 to 1.28)</b>	<b>1.26 (1.23 to 1.29)</b>	<b>1.23 (1.20 to 1.26)</b>
First diagnostic age of atopic dermatitis, years							
Comparator**	557,168	106,891	3,964,496	26.96	1.0 (reference)	1.0 (reference)	1.0 (reference)
<2	188,758	43,086	1,326,656	32.48	<b>1.22 (1.21 to 1.24)</b>	<b>1.22 (1.20 to 1.23)</b>	<b>1.19 (1.18 to 1.21)</b>
Comparator**	333,647	54,599	1,619,416	33.72	1.0 (reference)	1.0 (reference)	1.0 (reference)

2-4	105,665	19,079	520,714	36.64	<b>1.09 (1.08 to 1.11)</b>	<b>1.10 (1.08 to 1.12)</b>	<b>1.08 (1.06 to 1.10)</b>
Comparator**	136,988	8464	300,475	28.17	1.0 (reference)	1.0 (reference)	1.0 (reference)
≥5	48,178	3264	113,486	28.76	<b>1.05 (1.03 to 1.08)</b>	<b>1.05 (1.03 to 1.08)</b>	<b>1.03 (1.01 to 1.06)</b>

206     Abbreviation: CI, confidence interval.

207     \*Fracture incidence rate is expressed per 1,000 person-years

208     §Model 1 was adjusted for infant sex, calendar period of birth (2008–2010, 2011–2012, and 2013–2015), birth season (spring, summer, autumn,  
209     and winter), region of residence (rural and urban), household income (high, middle, and low), breastfeeding, preterm birth, and low birth weight.

210     ‡Model 2 was adjusted for infant sex, calendar period of birth (2008–2010, 2011–2012, and 2013–2015), birth season (spring, summer, autumn,  
211     and winter), region of residence (rural and urban), household income (high, middle, and low), breastfeeding, preterm birth, low birth weight,  
212     allergic rhinitis, asthma, diabetes mellitus, thyroid disorder, chronic inflammatory disease, chronic kidney disease, chronic neurological disorder,  
213     anemia, neuropsychiatric disorder, food allergy, and long-term use of systemic corticosteroids.

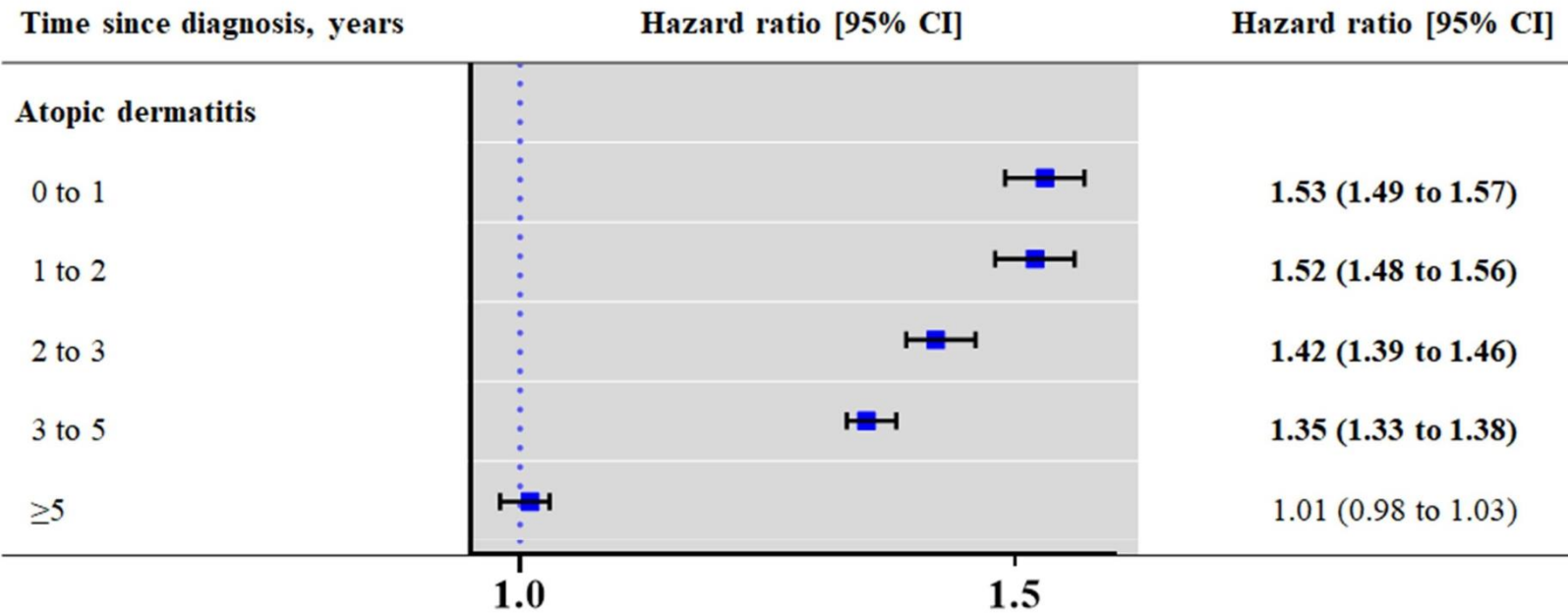
214     \*\*Comparators defined only 1:3 matched comparators in each patient group to reduce immortal time bias.

215     Statistically significant values (p>0.05) are shown in bold.

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217     **Figure 1.** Adjusted HR for the likelihood of incident fracture at different time points after AD diagnosis. Blue dots indicate adjusted HR for AD;

218 red dots indicate adjusted HR for FA; Whiskers represent 95% CIs. AD, atopic dermatitis; CI, confidence interval; HR, hazard ratio.



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221 Table S1. Demographic and clinical characteristics of participants in the Korean nationwide birth cohort

Characteristic	Full unmatched cohort	1:3 propensity-score-matched cohort		SMD
		Atopic dermatitis	Control	
Total, n (%)	1,778,588 (100)	342,601	1,027,803	
<b>Baseline characteristics</b>				
Infant sex, n (%)				< 0.001
Female	858,246 (48.3)	159,214 (46.5)	477,527 (46.5)	
Male	920,342 (51.8)	183,387 (53.5)	550,276 (53.5)	
Calendar period of birth, n (%)				< 0.001
2008-2010	626,542 (35.2)	129,324 (37.8)	387,871 (37.7)	
2011-2012	549,032 (30.9)	107,213 (31.3)	321,746 (31.3)	



2013-2015	603,014 (33.9)	106,064 (31.0)	318,186 (31.0)	
Birth season				< 0.001
Spring (March to May)	439,627 (24.7)	83,021 (24.2)	249,055 (24.2)	
Summer (June to August)	405,488 (22.8)	77,758 (22.7)	233,203 (22.7)	
Autumn (September to November)	467,929 (26.3)	91,621 (26.7)	274,950 (26.8)	
Winter (December to February)	465,544 (26.2)	90,201 (26.3)	270,595 (26.3)	
Region of residence, n (%)				< 0.001
Rural	959,202 (53.9)	187,308 (54.7)	561,890 (54.7)	
Urban	819,386 (46.1)	155,293 (45.3)	465,913 (45.3)	
Household income, n (%)				< 0.001

High (70 to 100th percentile)	766,662 (43.11)	143,403 (41.9)	430,274 (41.9)	
Middle (30 to 69th percentile)	724,898 (40.76)	141,552 (41.3)	424,578 (41.3)	
Low (0 to 29th percentile)	287,028 (16.14)	57,646 (16.8)	172,951 (16.8)	
Breastfeeding, yes, n (%)	1,072,794 (60.3)	209,150 (61.1)	627,355 (61.0)	< 0.001
Preterm birth, ≤ 36 week, n (%)	50,615 (2.9)	9660 (2.8)	28,660 (2.8)	0.002
Low birth weight, ≤2499g, n (%)	38,791 (2.2)	7181 (2.1)	21,200 (2.1)	0.002
<b>Diseases history and medication use during the observation period, n (%)</b>				
Allergic rhinitis	1,304,819 (73.4)	276,335 (80.7)	736,306 (71.6)	
Asthma	532,958 (30.0)	127,937 (37.3)	289,353 (28.2)	
Diabetes mellitus	48,721 (2.7)	11,577 (3.4)	26,289 (2.6)	
Thyroid disorder	19,392 (1.1)	4395 (1.3)	10,624 (1.0)	

Chronic inflammatory disease	18,542 (1.0)	4384 (1.3)	10,013 (1.0)	
Chronic kidney disease	7153 (0.4)	1810 (0.5)	3767 (0.4)	
Chronic neurologic disorder	43,617 (2.5)	9320 (2.7)	24,467 (2.4)	
Anemia	213,189 (12.0)	49,492 (14.5)	117,167 (11.4)	
Neuropsychiatric disorder	38,149 (2.14)	9020 (2.6)	21,536 (2.1)	
Long-term use of systemic corticosteroids (>90 days)	853 (0.1)	348 (0.1)	348 (0.03)	

222 SMD, standardized mean difference.

223 An SMD of <0.1 indicates no major imbalance. All SMDs were <0.003 in each propensity score-matched cohort.

224 Propensity scores were obtained using a logistic regression model adjusted for sex and period of birth, birth season, region of residence,

225 household income, breastfeeding, preterm birth, and low birth weight).

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227 Table S2. Subgroup analysis to determine the relationship of atopic dermatitis with subsequent fractures at different locations in the full  
 228 unmatched cohort (n=1,778,588)

Subgroups	Fracture events	Hazard ratio (95% CI)		
		Crude	Model 1 <sup>§</sup>	Model 2 <sup>‡</sup>
<b>Atopic dermatitis</b>				
Head fractures	102,575			
Atopic dermatitis versus none	10,429	<b>1.17 (1.14 to 1.19)</b>	<b>1.15 (1.13 to 1.18)</b>	<b>1.13 (1.10 to 1.15)</b>
Mild atopic dermatitis versus none	9071	<b>1.16 (1.14 to 1.19)</b>	<b>1.15 (1.12 to 1.17)</b>	<b>1.12 (1.09 to 1.15)</b>
Moderate to severe atopic dermatitis versus none	1358	<b>1.21 (1.15 to 1.28)</b>	<b>1.21 (1.15 to 1.28)</b>	<b>1.18 (1.12 to 1.24)</b>
Spine fractures	721			
Atopic dermatitis versus none	182	<b>1.38 (1.17 to 1.63)</b>	<b>1.38 (1.16 to 1.63)</b>	<b>1.33 (1.13 to 1.58)</b>

Mild atopic dermatitis versus none	161	<b>1.39 (1.17 to 1.66)</b>	<b>1.38 (1.16 to 1.65)</b>	<b>1.34 (1.13 to 1.60)</b>
Moderate to severe atopic dermatitis versus none	21	1.31 (0.85 to 2.03)	1.31 (0.85 to 2.03)	1.26 (0.82 to 1.95)
Upper limb fractures	162,714			
Atopic dermatitis versus none	33,968	<b>1.09 (1.07 to 1.10)</b>	<b>1.08 (1.07 to 1.09)</b>	<b>1.06 (1.05 to 1.07)</b>
Mild atopic dermatitis versus none	29,817	<b>1.09 (1.07 to 1.10)</b>	<b>1.08 (1.06 to 1.09)</b>	<b>1.06 (1.05 to 1.07)</b>
Moderate to severe atopic dermatitis versus none	4151	<b>1.08 (1.05 to 1.11)</b>	<b>1.08 (1.04 to 1.11)</b>	<b>1.06 (1.03 to 1.09)</b>
Lower limb fractures	90,128			
Atopic dermatitis versus none	20,031	<b>1.17 (1.15 to 1.19)</b>	<b>1.16 (1.14 to 1.18)</b>	<b>1.13 (1.12 to 1.15)</b>
Mild atopic dermatitis versus none	17,561	<b>1.16 (1.15 to 1.18)</b>	<b>1.16 (1.14 to 1.18)</b>	<b>1.13 (1.11 to 1.15)</b>
Moderate to severe atopic dermatitis versus none	2470	<b>1.19 (1.14 to 1.23)</b>	<b>1.18 (1.14 to 1.23)</b>	<b>1.15 (1.11 to 1.20)</b>

Other fractures	3591			
Atopic dermatitis versus none	819	<b>1.20 (1.11 to 1.30)</b>	<b>1.19 (1.10 to 1.28)</b>	<b>1.14 (1.05 to 1.23)</b>
Mild atopic dermatitis versus none	727	<b>1.21 (1.11 to 1.31)</b>	<b>1.20 (1.10 to 1.30)</b>	<b>1.145 (1.06 to 1.24)</b>
Moderate to severe atopic dermatitis versus none	92	1.12 (0.91 to 1.38)	1.13 (0.92 to 1.39)	1.08 (0.87 to 1.32)

229 CI, confidence interval.

230 §Model 1 was adjusted for infant sex, calendar period of birth (2008–2010, 2011–2012, and 2013–2015), birth season (spring, summer, autumn,  
231 and winter), region of residence (rural and urban), household income (high, middle, and low), breastfeeding, preterm birth, and low birth weight.

232 ‡Model 2 was adjusted for infant sex, calendar period of birth (2008–2010, 2011–2012, and 2013–2015), birth season (spring, summer, autumn,  
233 and winter), region of residence (rural and urban), household income (high, middle, and low), breastfeeding, preterm birth, low birth weight,  
234 allergic rhinitis, asthma, diabetes mellitus, thyroid disorder, chronic inflammatory disease, chronic kidney disease, chronic neurological disorder,  
235 anemia, neuropsychiatric disorder, and long-term use of systemic corticosteroids.

236 Statistically significant values ( $p < 0.05$ ) are shown in bold.

237 Table S3. Stratification analysis to determine the relationship of atopic dermatitis with subsequent overall fracture and stratification by  
 238 participants' sex, calendar period of birth, region of residence, and breastfeeding history in the full unmatched cohort (n=1,778,588)

					Hazard ratio (95% CI)		
Stratification analysis	Exposure	Outcome	Fracture incidence rate* (non-exposure)	Fracture incidence rate* (exposure)	Crude	Model 1 <sup>§</sup>	Model 2 <sup>‡</sup>
Infant sex							
Male	Atopic dermatitis	Fracture	25.21	28.10	<b>1.12 (1.06 to 1.19)</b>	<b>1.12 (1.06 to 1.19)</b>	<b>1.08 (1.02 to 1.15)</b>
Female	Atopic dermatitis	Fracture	19.08	21.86	<b>1.18 (1.09 to 1.27)</b>	<b>1.17 (1.08 to 1.26)</b>	<b>1.13 (1.04 to 1.22)</b>
Calendar period of birth							
2008-2010	Atopic dermatitis	Fracture	25.71	29.01	<b>1.13 (1.12 to 1.15)</b>	<b>1.12 (1.11 to 1.14)</b>	<b>1.10 (1.09 to 1.11)</b>
2011-2012	Atopic dermatitis	Fracture	21.22	23.59	<b>1.11 (1.10 to 1.13)</b>	<b>1.11 (1.09 to 1.12)</b>	<b>1.08 (1.07 to 1.10)</b>

2013-2015	Atopic dermatitis	Fracture	17.57	19.59	<b>1.12 (1.09 to 1.14)</b>	<b>1.11 (1.09 to 1.13)</b>	<b>1.09 (1.07 to 1.12)</b>
Region of residence							
Rural	Atopic dermatitis	Fracture	22.33	25.10	<b>1.11 (1.10 to 1.13)</b>	<b>1.11 (1.09 to 1.12)</b>	<b>1.08 (1.07 to 1.10)</b>
Urban	Atopic dermatitis	Fracture	22.05	25.26	<b>1.14 (1.12 to 1.15)</b>	<b>1.13 (1.11 to 1.14)</b>	<b>1.10 (1.09 to 1.12)</b>
Breastfeeding							
Yes	Atopic dermatitis	Fracture	22.57	25.58	<b>1.12 (1.11 to 1.14)</b>	<b>1.12 (1.11 to 1.13)</b>	<b>1.09 (1.08 to 1.11)</b>
No	Atopic dermatitis	Fracture	21.63	24.52	<b>1.12 (1.11 to 1.14)</b>	<b>1.11 (1.10 to 1.13)</b>	<b>1.09 (1.08 to 1.11)</b>
Birth season							
Spring to summer	Atopic dermatitis	Fracture	28.88	33.14	<b>1.15 (1.14 to 1.17)</b>	<b>1.15 (1.14 to 1.17)</b>	<b>1.13 (1.11 to 1.14)</b>
Autumn to winter	Atopic dermatitis	Fracture	28.89	33.57	<b>1.17 (1.15 to 1.18)</b>	<b>1.17 (1.15 to 1.18)</b>	<b>1.14 (1.13 to 1.16)</b>

239 CI, confidence interval.

240 \*Fracture incidence rate is expressed per 1,000 person-years.



241 §Model 1 was adjusted for infant sex, calendar period of birth (2008–2010, 2011–2012, and 2013–2015), birth season (spring, summer, autumn,  
242 and winter), region of residence (rural and urban), household income (high, middle, and low), breastfeeding, preterm birth, and low birth weight.

243 ‡Model 2 was adjusted for infant sex, calendar period of birth (2008–2010, 2011–2012, and 2013–2015), birth season (spring, summer, autumn,  
244 and winter), region of residence (rural and urban), household income (high, middle, and low), breastfeeding, preterm birth, low birth weight,  
245 allergic rhinitis, asthma, diabetes mellitus, thyroid disorder, chronic inflammatory disease, chronic kidney disease, chronic neurological disorder,  
246 anemia, neuropsychiatric disorder, and long-term use of systemic corticosteroids.

247 Statistically significant values ( $p < 0.05$ ) are shown in bold.

248

249 Table S4. Various association of atopic dermatitis with subsequent other disease in propensity score-matched cohort (n=1,370,404)

Exposure	Outcome	Hazard ratio (95% CI)		Association
		Crude	Model*	
Atopic dermatitis	Diabetes mellitus	<b>1.222 (1.196 to 1.249)</b>	<b>1.192 (1.166 to 1.219)</b>	
	Thyroid disorder	<b>1.06 (1.022 to 1.099)</b>	1.021 (0.985 to 1.059)	Null association
	Chronic inflammatory disease	<b>1.234 (1.193 to 1.277)</b>	<b>1.210 (1.170 to 1.252)</b>	
	Chronic kidney disease	<b>1.068 (1.008 to 1.131)</b>	1.019 (0.962 to 1.080)	Null association
	Chronic neurologic disorder	<b>1.155 (1.128 to 1.184)</b>	<b>1.124 (1.097 to 1.151)</b>	
	Anemia	<b>1.106 (1.093 to 1.119)</b>	<b>1.084 (1.071 to 1.097)</b>	
	Neuropsychiatric disorder	<b>1.085 (1.059 to 1.111)</b>	<b>1.064 (1.038 to 1.089)</b>	

250 CI, confidence interval.

251 \* Model 2 was adjusted for infant sex, calendar period of birth (2008–2010, 2011–2012, and 2013–2015), birth season (spring, summer, autumn,  
252 and winter), region of residence (rural and urban), household income (high, middle, and low), breastfeeding, preterm birth, low birth weight,  
253 allergic rhinitis, asthma, diabetes mellitus, thyroid disorder, chronic inflammatory disease, chronic kidney disease, chronic neurological disorder,  
254 anemia, neuropsychiatric disorder, and long-term use of systemic corticosteroids.

255 Statistically significant values ( $p < 0.05$ ) are shown in bold.

