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

**To the Editor**

Previous studies have determined the relationship between atopic dermatitis (AD) and the risk of fractures.1-3 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.1-3 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 Korea4 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])3. By default, all children were classified as having mild AD unless they were treated with the immunosuppressants mentioned above while presenting moderate to severe AD3.

The primary outcome was the first diagnosis of fracture based on the appropriate ICD-10 code5,6. 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.5

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).7 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.8

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.1-3,8

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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Table 1. Cox proportional hazards model to determine the relationship of atopic dermatitis with subsequent overall bone fracture in full 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§ | Model 2‡ |
| Full unmatched cohort (n=1,778,588) | | | | | | | |
| **Atopic dermatitis** |  |  |  |  |  |  |  |
| 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 | **1.12 (1.11 to 1.13)** | **1.12 (1.11 to 1.13)** | **1.09 (1.08 to 1.10)** |
| 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 | **1.12 (1.11 to 1.13)** | **1.11 (1.10 to 1.12)** | **1.09 (1.08 to 1.10)** |
| Moderate to severe atopic dermatitis | 43,864 | 8092 | 325,081 | 24.89 | **1.13 (1.11 to 1.16)** | **1.13 (1.11 to 1.16)** | **1.11 (1.08 to 1.13)** |
| 1:3 propensity score-matched cohort (n=1,370,404) | | | | | | | |
| **Atopic dermatitis** |  |  |  |  |  |  |  |
| 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 | **1.16 (1.15 to 1.17)** | **1.16 (1.15 to 1.17)** | **1.14 (1.13 to 1.15)** |
| 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 | **1.15 (1.14 to 1.16)** | **1.15 (1.14 to 1.16)** | **1.12 (1.11 to 1.14)** |
| Moderate to severe atopic dermatitis | 43,864 | 8092 | 227,659 | 35.54 | **1.25 (1.22 to 1.28)** | **1.26 (1.23 to 1.29)** | **1.23 (1.20 to 1.26)** |
| 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 | **1.22 (1.21 to 1.24)** | **1.22 (1.20 to 1.23)** | **1.19 (1.18 to 1.21)** |
| 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 | **1.09 (1.08 to 1.11)** | **1.10 (1.08 to 1.12)** | **1.08 (1.06 to 1.10)** |
| 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 | **1.05 (1.03 to 1.08)** | **1.05 (1.03 to 1.08)** | **1.03 (1.01 to 1.06)** |

Abbreviation: CI, confidence interval.

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

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

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

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

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

**Figure 1.** Adjusted HR for the likelihood of incident fracture at different time points after AD diagnosis. Blue dots indicate adjusted HR for AD; red dots indicate adjusted HR for FA; Whiskers represent 95% CIs. AD, atopic dermatitis; CI, confidence interval; HR, hazard ratio.

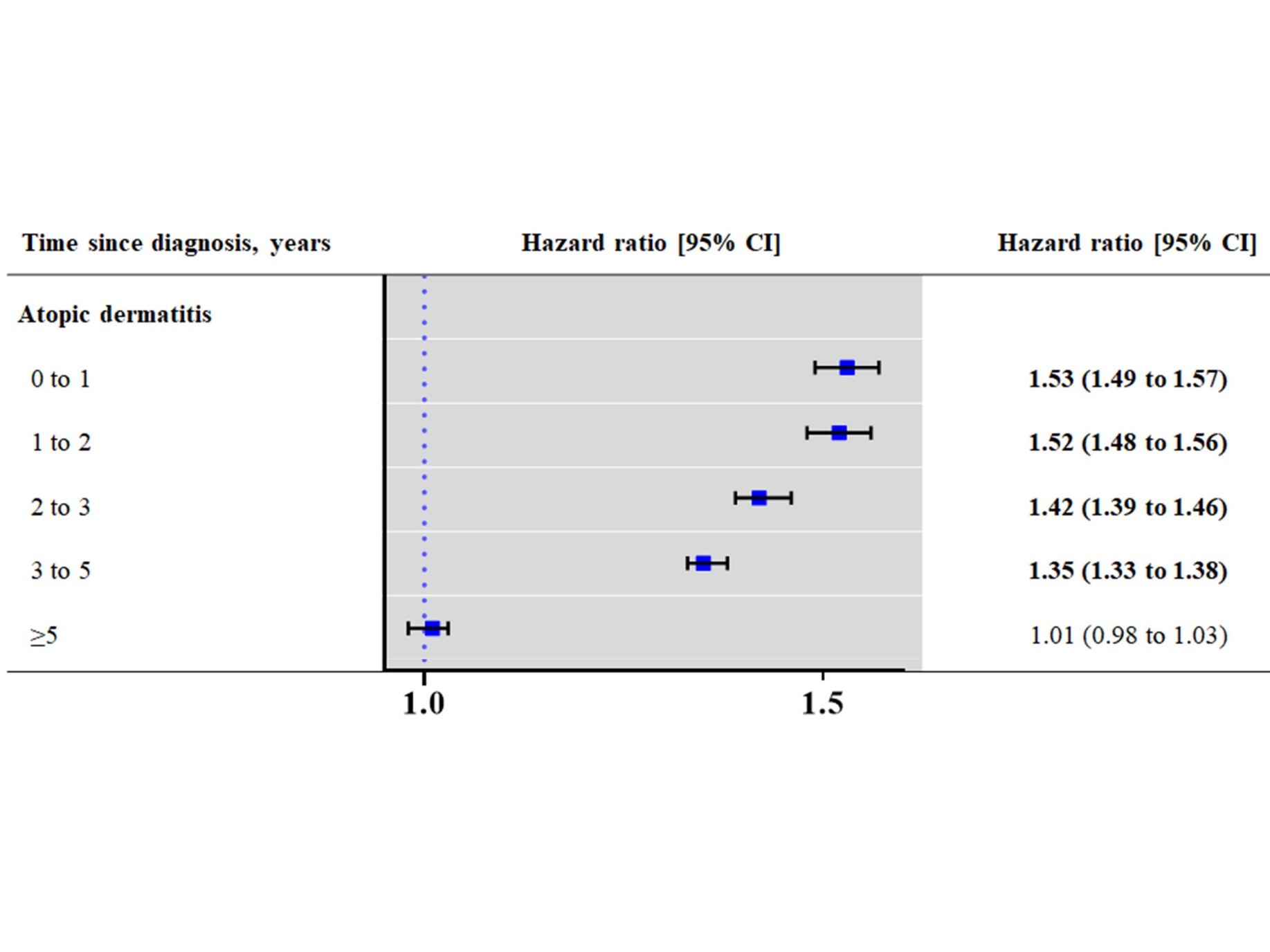


Table S1. Demographic and clinical characteristics of participants in the Korean nationwide birth cohort

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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 |  |
| **Baseline characteristics** |  |  |  |  |
| 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 |
| **Diseases history and medication use during the observation period, n (%)** |  |  |  |  |
| 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) |  |

SMD, standardized mean difference.

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

Propensity scores were obtained using a logistic regression model adjusted for sex and period of birth, birth season, region of residence, household income, breastfeeding, preterm birth, and low birth weight).

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Subgroups | Fracture events | Hazard ratio (95% CI) | | |
| Crude | Model 1§ | Model 2‡ |
| **Atopic dermatitis** |  |  |  |  |
| Head fractures | 102,575 |  |  |  |
| Atopic dermatitis versus none | 10,429 | **1.17 (1.14 to 1.19)** | **1.15 (1.13 to 1.18)** | **1.13 (1.10 to 1.15)** |
| Mild atopic dermatitis versus none | 9071 | **1.16 (1.14 to 1.19)** | **1.15 (1.12 to 1.17)** | **1.12 (1.09 to 1.15)** |
| Moderate to severe atopic dermatitis versus none | 1358 | **1.21 (1.15 to 1.28)** | **1.21 (1.15 to 1.28)** | **1.18 (1.12 to 1.24)** |
| Spine fractures | 721 |  |  |  |
| Atopic dermatitis versus none | 182 | **1.38 (1.17 to 1.63)** | **1.38 (1.16 to 1.63)** | **1.33 (1.13 to 1.58)** |
| Mild atopic dermatitis versus none | 161 | **1.39 (1.17 to 1.66)** | **1.38 (1.16 to 1.65)** | **1.34 (1.13 to 1.60)** |
| 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 | **1.09 (1.07 to 1.10)** | **1.08 (1.07 to 1.09)** | **1.06 (1.05 to 1.07)** |
| Mild atopic dermatitis versus none | 29,817 | **1.09 (1.07 to 1.10)** | **1.08 (1.06 to 1.09)** | **1.06 (1.05 to 1.07)** |
| Moderate to severe atopic dermatitis versus none | 4151 | **1.08 (1.05 to 1.11)** | **1.08 (1.04 to 1.11)** | **1.06 (1.03 to 1.09)** |
| Lower limb fractures | 90,128 |  |  |  |
| Atopic dermatitis versus none | 20,031 | **1.17 (1.15 to 1.19)** | **1.16 (1.14 to 1.18)** | **1.13 (1.12 to 1.15)** |
| Mild atopic dermatitis versus none | 17,561 | **1.16 (1.15 to 1.18)** | **1.16 (1.14 to 1.18)** | **1.13 (1.11 to 1.15)** |
| Moderate to severe atopic dermatitis versus none | 2470 | **1.19 (1.14 to 1.23)** | **1.18 (1.14 to 1.23)** | **1.15 (1.11 to 1.20)** |
| Other fractures | 3591 |  |  |  |
| Atopic dermatitis versus none | 819 | **1.20 (1.11 to 1.30)** | **1.19 (1.10 to 1.28)** | **1.14 (1.05 to 1.23)** |
| Mild atopic dermatitis versus none | 727 | **1.21 (1.11 to 1.31)** | **1.20 (1.10 to 1.30)** | **1.145 (1.06 to 1.24)** |
| 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) |

CI, confidence interval.

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

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

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

Table S3. Stratification analysis to determine the relationship of atopic dermatitis with subsequent overall fracture and stratification by 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§ | Model 2‡ |
| Infant sex |  |  |  |  |  |  |  |
| Male | Atopic dermatitis | Fracture | 25.21 | 28.10 | **1.12 (1.06 to 1.19)** | **1.12 (1.06 to 1.19)** | **1.08 (1.02 to 1.15)** |
| Female | Atopic dermatitis | Fracture | 19.08 | 21.86 | **1.18 (1.09 to 1.27)** | **1.17 (1.08 to 1.26)** | **1.13 (1.04 to 1.22)** |
| Calendar period of birth |  |  |  |  |  |  |  |
| 2008-2010 | Atopic dermatitis | Fracture | 25.71 | 29.01 | **1.13 (1.12 to 1.15)** | **1.12 (1.11 to 1.14)** | **1.10 (1.09 to 1.11)** |
| 2011-2012 | Atopic dermatitis | Fracture | 21.22 | 23.59 | **1.11 (1.10 to 1.13)** | **1.11 (1.09 to 1.12)** | **1.08 (1.07 to 1.10)** |
| 2013-2015 | Atopic dermatitis | Fracture | 17.57 | 19.59 | **1.12 (1.09 to 1.14)** | **1.11 (1.09 to 1.13)** | **1.09 (1.07 to 1.12)** |
| Region of residence |  |  |  |  |  |  |  |
| Rural | Atopic dermatitis | Fracture | 22.33 | 25.10 | **1.11 (1.10 to 1.13)** | **1.11 (1.09 to 1.12)** | **1.08 (1.07 to 1.10)** |
| Urban | Atopic dermatitis | Fracture | 22.05 | 25.26 | **1.14 (1.12 to 1.15)** | **1.13 (1.11 to 1.14)** | **1.10 (1.09 to 1.12)** |
| Breastfeeding |  |  |  |  |  |  |  |
| Yes | Atopic dermatitis | Fracture | 22.57 | 25.58 | **1.12 (1.11 to 1.14)** | **1.12 (1.11 to 1.13)** | **1.09 (1.08 to 1.11)** |
| No | Atopic dermatitis | Fracture | 21.63 | 24.52 | **1.12 (1.11 to 1.14)** | **1.11 (1.10 to 1.13)** | **1.09 (1.08 to 1.11)** |
| Birth season |  |  |  |  |  |  |  |
| Spring to summer | Atopic dermatitis | Fracture | 28.88 | 33.14 | **1.15 (1.14 to 1.17)** | **1.15 (1.14 to 1.17)** | **1.13 (1.11 to 1.14)** |
| Autumn to winter | Atopic dermatitis | Fracture | 28.89 | 33.57 | **1.17 (1.15 to 1.18)** | **1.17 (1.15 to 1.18)** | **1.14 (1.13 to 1.16)** |

CI, confidence interval.

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

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

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

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

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

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

CI, confidence interval.

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

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