

## ORIGINAL ARTICLE

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# Association of clinical and social factors with risk of fracture in children with atopic dermatitis

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## Abstract

**Background:** Children with atopic dermatitis (AD) have multiple risk factors for accidental fractures, injuries that can lead to significant morbidity and mortality. However, little is known about the factors that mediate the relationship between AD and fracture in children.

**Objective:** Our purpose was to examine the association of AD with fracture and to identify potential mediating factors.

**Methods:** This retrospective cohort study examined children with and without AD from a longitudinal matched cohort database of 353,040 children registered in the national health insurance service and participated in the national health-screening program of Korea. We defined AD using medical claims and medication prescription records. We investigated accidental fracture events between the index date and the end of follow-up in a propensity score-matched cohort. Pre-specified subgroup analyses considered fractures in four different regions of the body. The mediating effects of 10 possible clinical factors (including the use of antihistamines and systemic corticosteroids) and social factors (including nutritional status and parental safety awareness) were determined.

**Results:** There were 145,704 participating children, 20% with AD and 49% girls. Fractures occurred in 6,652 of the children with AD (23%, mean age:  $64.6 \pm 29.2$  months) and in 24,698 of the control group (21%, mean age  $65.0 \pm 28.9$  months). Children with AD had an 8% greater risk of fracture events overall (adjusted relative risk [aRR]: 1.08, 95% CI: 1.05–1.10). In subgroup analysis, AD was related to increased rates of skull and facial bone fracture (aRR: 1.09, 95% CI: 1.04–1.14), for trunk including vertebrae (aRR: 1.58, 95% CI: 1.22–2.05), and for distal limbs (aRR: 1.11, 95% CI: 1.07–1.15). However, the relationship with proximal limb fracture was insignificant. Duration of systemic corticosteroid prescription was the largest mediating factor, followed by duration of antihistamine prescription, and infant feeding practices. In particular, the duration of systemic corticosteroid prescription was significantly associated with fracture events (incidence: 20.1% at the 25th percentile and 23.6% at the 75th percentile; difference: 3.4% [95% CI: 2.8–4.0%]).

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**Conclusions:** Children with AD were related to increased fracture events. The key factors with mediating effects were systemic use of corticosteroid and antihistamine. Infant feeding practices had weaker mediating effects.

**KEYWORDS**

allergy diagnosis, atopic dermatitis, fracture, pediatrics, population characteristics

## 1 | INTRODUCTION

Fractures are common extremity injuries and a leading reason for hospital admission,<sup>1,2</sup> especially in children and the elderly.<sup>1,3</sup> Fractures in children can be expensive to treat, can delay normal development, and may even lead to permanent disability.<sup>1,4</sup> For these reasons, it is necessary to determine the incidence of childhood fractures and to identify the underlying causes.

Atopic dermatitis (AD), a common inflammatory skin disease that affects 15%–30% of all children,<sup>5,6</sup> may be associated with unfavorable bone health. Studies of adults reported that the increased risk for fracture in those with inadequately controlled AD is linked to the use of systemic corticosteroids and the consequent decreased bone mineral density.<sup>7,8</sup> Indeed, previous studies reported that AD in children was associated with poor bone health, similar to other chronic inflammatory diseases, but the relationship between childhood AD and risk of fracture remains unexplored. Some studies indicated that AD in children was associated with clinical manifestations and complications aside from skin inflammation, such as sleep disorders, neuropsychiatric disease,<sup>9</sup> allergic comorbidities, poor nutritional status,<sup>10,11</sup> and musculoskeletal injuries.<sup>11</sup> Considering these complications of AD, it is clearly important to identify the association between AD and other clinical conditions.

The purpose of this study was to use a large national population-based data set that included stratified questionnaires and information on healthcare utilization to determine the association of AD with the risk of fractures in children and to identify factors that mediate this relationship. This is an important extension of earlier research for several important reasons. We used a large, nationwide longitudinal representative sample; we thoroughly assessed detailed information regarding family income, residency, and perinatal conditions; and we utilized information on birth history (birth weight, prematurity), type of feeding during infancy, nutritional status, physical examination findings at 4–6 months old, and parental safety awareness, obtained by the national health-screening program.

## 2 | METHODS

### 2.1 | Study design and participants

Data were from a cohort study conducted with a nationally representative sample of the Korean pediatric population and administrative records.<sup>12</sup> The date of AD diagnosis was defined as the index

### Key Message

- Fractures are common extremity injuries and a leading reason for hospital admission in children. Atopic dermatitis is one of the most common inflammatory skin diseases and may be associated with adverse bone health. Previous studies suggested that atopic dermatitis may reduce bone density, which might result in increased susceptibility to bone fracture; we tended to explore potential association of childhood atopic dermatitis with bone fracture.
- In our nationwide population-based cohort in children of South Korea, atopic dermatitis was associated with an increased risk for bone fracture. In particular, systemic corticosteroid use and antihistamine use were key factors with mediating effects associated with a greater risk for bone fractures.
- Altogether, our findings suggest that physicians should be aware in using medications and assessing the prognosis for patients with atopic dermatitis, who are in higher risks of childhood bone injury which might be more easily resulting in fracture.

date, and individuals were only assigned to the cohort once. Final assessment was on December 31, 2017, with a median of follow-up of 8.9 years (interquartile range [IQR]: 8.4, 9.4).

Information was from the national health insurance service (NHIS) database and the national screening program for infants and children (NHSPIC) (Table S1). The AD group consisted of individuals who received diagnoses of AD during the observation period (from birth until December 31, 2017). AD was defined using ICD-10 codes from the NHIS registry database, with at least five inpatient or outpatient claims for L20, and at least two records of prescriptions for AD-related medications. A recent longitudinal cohort study suggested that this diagnostic algorithm provided very good sensitivity, specificity, and positive predictive values, thus confirming its validity, and found that it strongly correlated with clinical examination results.<sup>13</sup> The control group consisted of individuals who did not have AD during the observation period.

We performed propensity score matching to reduce potential confounding effects and balance the baseline characteristics between the AD group and control groups. In detail, we conducted

1:4 propensity score (PS) matching using 38 factors including birth history and perinatal medical conditions that were previously documented to affect bone density and fracture during infancy. Age at the first diagnosis of fracture was defined by the age of the child when the first ICD-10 code was recorded in the administrative registry in all individuals who experienced at least one fracture. All fractures that occurred at least 6 months after the index date were identified. Medications taken between the index date and the first fracture were identified. Controls were randomly assigned an index date (simulated date of an AD diagnosis), so that the control and AD groups had the same distributions of index dates. Within the matched cohort, individuals without fracture were also randomly assigned a simulated date of the first fracture, so that the two groups had the same distributions of event dates (Figure S1). All individuals included in the analytic cohort participated in the national health-screening program between the ages of 4 and 6 months.

The Institutional Review Board of the Korea National Institute for Bioethics Policy approved this study (P01-201603-21-005).

## 2.2 | Outcomes

The main outcome of interest was fracture by any cause, as identified in the hospital records. Information about fracture diagnoses was from ICD-10 codes in the NHIS database. We examined alternative definitions of fracture as sensitivity analyses, in which medical codes were for splint or cast application. Thus, we used two alternative definitions of fracture: (i) any inpatient or outpatient visit with a diagnosis of fracture (ie, all relevant diagnostic codes considered, even if it was not the main diagnosis) and (ii) any hospital visit with a relevant diagnostic code that had a service code of splint application.

We conducted analysis of fractures in the four different body regions by including an interaction term in the model. Analyses were conducted using two different classifications by affected body parts where the fracture occurred by (i) skull and facial bones; (ii) trunk including vertebrae; (iii) proximal limbs; and (iv) distal limb, and by (i) head and neck; (ii) trunk; (iii) upper extremity; and (iv) lower extremity.

We conducted additional subgroup analysis stratified by age when fracture occurred (at 2–4 and  $\geq 5$  years of age). We also repeated the main analysis of fracture rates stratified by affected body parts that are known to be more fractured by accidental injury, non-accidental injury, and decreased bone density in children.<sup>14–16</sup>

## 2.3 | Potential mediating factors

Factors with previously documented evidence of influence on fracture, or association with accidental events was selected as potential mediating factors (Table 1). Mediation analysis was performed

to assess the association of 10 potential factors including clinical factors (including the use of antihistamines and systemic corticosteroids) and social factors (including nutritional status and parental safety awareness) (Tables S2 and S3) in mediating the relationship of AD with fracture. Continuous variables were inverted as necessary so that a higher value for each variable was inversely associated with the risk of fracture. Likewise, dichotomous factors were defined so the presence of the factor was associated with higher risk of fracture.

## 2.4 | Analysis

We used propensity score (PS) matching to balance for differences in covariates including baseline and clinical conditions of the AD and control groups. This included 13 perinatal demographic characteristics and medical conditions (Table S4) and 25 binary factors (Table S5). Differences between groups were compared using standardized differences in both the unmatched and matched samples, and differences  $>10\%$  were considered significant. Number of events, follow-up time, prevalence, risk ratios (RRs), and 95% confidence interval (CI) were calculated for the outcome throughout the observation period. Risks ratios (RRs) and 95% confidence intervals (CIs) of the outcome were calculated using modified Poisson regression with a log-link function; subgroups with fractures in different body regions were also analyzed. Model was adjusted for confounders, which included birth year, certain conditions originating during the perinatal period, physical examination results at 4–6 months old, clinical conditions with possible confounding effects (Table S6), date of first AD diagnosis, and first recorded fracture diagnosis. Data analysis was performed using SAS Enterprise Guide version 7.1 (SAS Institute Inc.).

We performed mediation analysis to estimate the proportion of association (the association of AD with incident fracture) that is attributable to mediating factors (the 10 factors in Table 1). To estimate the “indirect effect” of the presence of AD on incident fracture through each potential mediator, we calculated the difference between the total effect of AD on fracture and the “direct effect” of AD on incident fracture after adjusting for the intermediate variable, examining each individual intermediate variable in separate models. Next, we estimated the indirect effect of AD mediated through all potential mediators by calculating the difference between the coefficient of total effect of AD on incident fracture and the coefficient of direct effect of AD on incident fracture after adjusting for the intermediate variable, from a model adjusting for confounders. We placed causal mediation analysis within the counterfactual framework of causal inference. We assessed the magnitude of each factor in mediating the association of AD and incident fracture by this approach.

We performed pre-specified analyses with stratification by parts of fracture and age when the event occurred to assess age or parts of body affected as effect modifiers of the difference in the risk of fracture in participants with and without AD. Analyses were conducted using R (version 3.1.1).

TABLE 1 Potential mediating factors measured at baseline

| Potential mediating factor                | Source                                                                                                                                                                              | Classification <sup>a</sup>                                                                                                                          |
|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Birth weight                              | Answer (by parents) to questionnaire item at the first round of the national health-screening program                                                                               | Continuous variable (range: 2.6–3.9)                                                                                                                 |
| Weight for age at 4–6 months <sup>b</sup> | Measured at the first round of the national health-screening program                                                                                                                | Continuous variable (range: 3.6–15)                                                                                                                  |
| Birth residence                           | Eligibility database                                                                                                                                                                | Dichotomized as Seoul/metropolitan vs. city/rural                                                                                                    |
| Household income                          | Amount of insurance co-payment in the eligibility database                                                                                                                          | Quintiles, with higher score indicating lower income                                                                                                 |
| Infant feeding practice                   | Answer (by parents) to questionnaire item about types of feeding at 4–6 months of age, reported in selected categories at the first round of the national health-screening program  | Dichotomized as breast feeding <sup>c</sup> vs. feeding types other than breast feeding (bottle feeding; mixed feeding; and special formula feeding) |
| Unfavorable nutritional status            | Answer (by parents) to questionnaire item about types and ranges of food the child ate, reported in selected categories at the first round of the national health-screening program | Continuous variable (range: 0–6), with higher score indicating unfavorable nutritional status                                                        |
| Parental safety awareness                 | Answers (by parents) to the safety-related questionnaire, reported in selected categories at the first round of the national health-screening program                               | Continuous variable (range: 0–5), with higher score indicating less awareness                                                                        |
| Systemic corticosteroid prescription      | Number of systemic corticosteroid prescriptions from NHIS claims-based data (1 point per 20 prescription days)                                                                      | Continuous variable (range: 0–4)                                                                                                                     |
| Antihistamine prescription                | Number of antihistamine prescriptions from NHIS claims-based data (1 point per 100 prescription days)                                                                               | Continuous variable (range: 0–4)                                                                                                                     |
| Methylphenidate prescription              | Number of methylphenidate prescriptions from NHIS claims-based data (1 point per 10 prescription days)                                                                              | Continuous variable (range: 0–4)                                                                                                                     |

Abbreviation: NHIS, national health insurance service.

<sup>a</sup>All mediating factors were defined or rescaled so that a higher value was presumably associated with a higher risk of fracture.

<sup>b</sup>Percentage of weight-for-age calculated using Korean national growth charts for children and adolescents.<sup>15</sup>

<sup>c</sup>Defined as exclusive breastfeeding during the first 4 months of age.

### 3 | RESULTS

#### 3.1 | Participants

Between January 1, 2008, and December 31, 2009, 919,707 children born in South Korea completed the screening program at the age of 4–6 months and had complete records on birth weight and other relevant parameters (Figure 1). Application of these inclusion and exclusion criteria led to an unmatched cohort consisting of 314,721 children without AD (89.1%) and 38,319 children with AD (10.9%). We initially examined the characteristics of individuals in the PS-matched cohort (Table 2). There were 116,542 children without AD and 29,162 children with AD in the matched cohort.

#### 3.2 | Association of AD with fracture rates

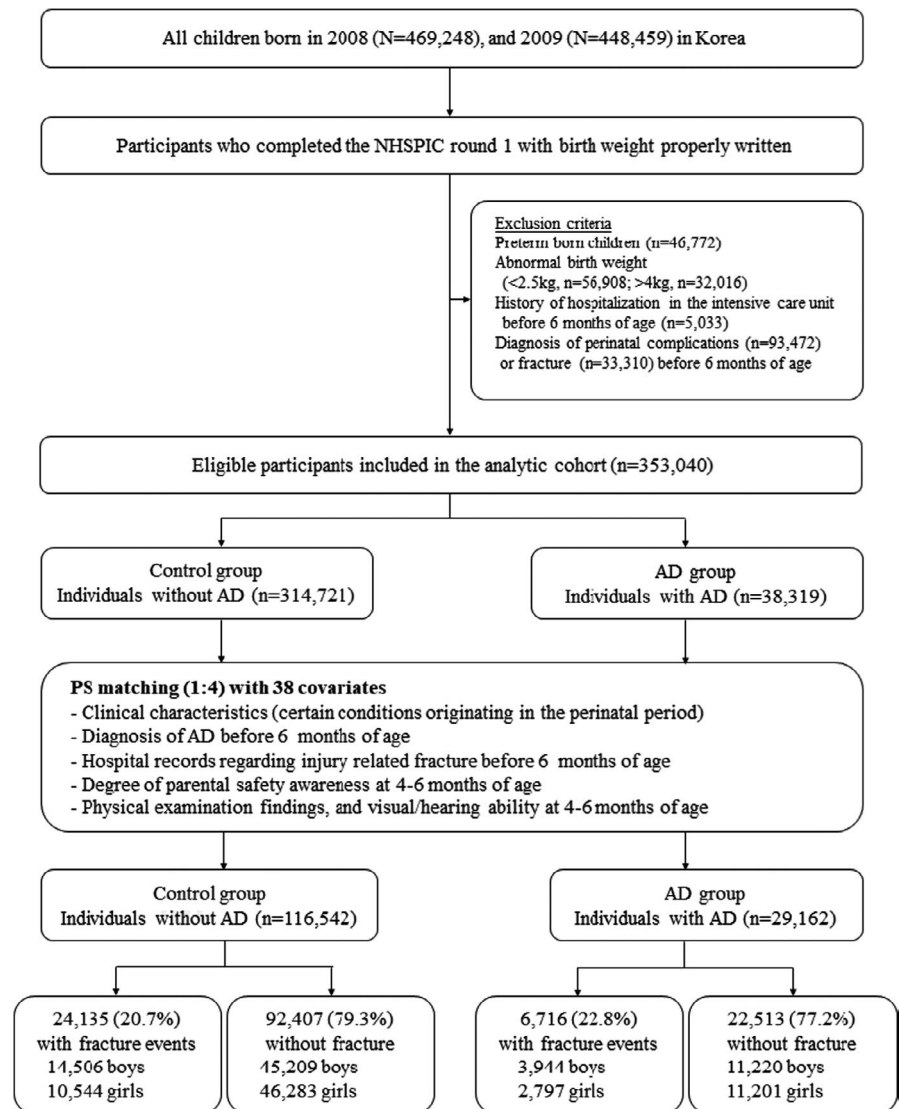
The prevalence of fracture events was 21.2% (95% CI: 21.0–21.4) in children without AD and 22.8% (95% CI: 22.3–23.3) in children with AD, with a median follow-up time of 8.9 years (IQR: 8.4, 9.4). After adjustment and PS matching for the 38 covariates, fracture rates were higher in children with AD relative to those without AD

(aRR: 1.08, 95% CI: 1.05–1.10) in children overall (Table 3). Higher rates were both shown in boys (aRR: 1.07, 95% CI: 1.04–1.10) and girls (aRR: 1.08, 95% CI: 1.04–1.12) (Table S7).

In pre-specified analysis, the results were consistent showing associations of AD and fracture, except for the proximal bones. The risks of fracture were significant in skull and facial bones (aRR: 1.09, 95% CI: 1.04–1.14), for trunk including vertebrae (aRR: 1.58, 95% CI: 1.22–2.05), and risk was strengthened in distal limbs (aRR: 1.11, 95% CI: 1.07–1.15). However, the association for proximal limb fracture was insignificant. In subgroup 2 divided as fracture occurred in head and neck, trunk, upper, and lower extremities, results were consistent presenting significantly increased rates of fracture in all parts investigated (Figure 2).

When we repeated the main analysis in different age groups, the results were consistent. The result showed that 1441 (4.9%) participants of the AD group experienced fracture, during the observation period (while the child was 2–4 years old) compared with 5184 (4.5%) of those of the controls (aRR 1.11, 95% CI: 1.05–1.18) (Table S8). When outcomes were defined as fracture that occurred after 5 ≥ years, and 1163 (4.0%) participants of the AD group experienced fracture, compared with 14,456 (12.4%) of those of the controls (aRR 1.07, 95% CI: 1.04–1.11) (Table S9).

**FIGURE 1** Study design and disposition of participating children from baseline to the analytic cohort



Finally, we repeated the main analysis in fracture divided by affected by subgroups of body parts where fracture occurred, categorized as bones more commonly affected by accidental injury, non-accidental injury, and decreased bone density (Table S10). In sites known to be easily fractured after accidental injury, participants of the AD group experienced more fracture during the observation period compared with the controls (3908 [13.0%] vs 14,079 [12.8%], aRR 1.11, 95%CI: 1.07–1.15). However, the association for increased rate outcomes in sites easily fractured after non-accidental injury (aRR 0.87, 95%CI: 0.62–1.23), or due to decreased bone density (aRR 0.67, 95%CI: 0.24–2.01) were insignificant.

### 3.3 | Effect of mediating factors

We then identified factors that mediated the relationship of AD with fracture (Table 4). The adjusted least-squares mean for systemic corticosteroid prescription was 47.1% (95% CI: 46.7%–47.5%) in the control group and 61.7% (95% CI: 60.9%–62.5%) in the AD group,

corresponding to a difference of 14.5% (95% CI: 13.7%–15.4%). Systemic corticosteroid prescription was significantly associated with fracture events (adjusted OR [aOR]: 1.20, 95% CI: 1.15–1.25) and the absolute risk difference in fracture was 3.1% (95% CI: 2.5–3.7). Corticosteroid prescription was the largest mediating factor and accounted for 28.6% (95% CI: 19.2–50.0) of the excess risk (Figure 2).

The adjusted least-squares mean for antihistamine prescription was 48.0% (95% CI: 47.6%–48.5%) in the control group and 57.3% (95% CI: 56.5%–58.1%) in the AD group; the adjusted difference in means was 9.2% (95% CI: 8.3%–10.1%). There was a significant association between antihistamine prescription and the risk of fracture events (aOR: 1.30, 95% CI: 1.23–1.37). Antihistamine prescription was the second-largest mediating factor, accounting for 19.6% (95% CI: 13.6–31.0) of the excess risk.

The adjusted least-squares mean for infantile feeding practices was 46.0% (95% CI: 45.7%–46.3%) in the control group and 49.7% (95% CI: 49.1%–50.3%) in the AD group; the adjusted difference in means was 3.7% (95% CI: 3.1%–4.4%). There was a significant

TABLE 2 Characteristics of participants with and without AD

|                                             |         | Control group |                  | AD group  |                  |
|---------------------------------------------|---------|---------------|------------------|-----------|------------------|
| Potential mediating factor                  | N       | Median, n     | % (IQR)          | Median, n | % (IQR)          |
| Birth weight                                |         |               |                  |           |                  |
| Total (N)                                   | 145,704 | 112,740       |                  | 29,162    |                  |
| Median (IQR)                                |         | 3.2           | (3.0, 3.5)       | 3.2       | (3.0,3.5)        |
| Weight for age at 4–6 months                |         |               |                  |           |                  |
| Total (N)                                   | 145,642 | 116,490       |                  | 29,152    |                  |
| Median (IQR)                                |         | 8.1           | (7.5, 8.8)       | 8.1       | (7.50,8.80)      |
| Birth residence                             |         |               |                  |           |                  |
| Seoul OR Metropolitan                       | 71,708  | 56,918        | 48.84%           | 14,790    | 50.72%           |
| City OR Rural                               | 72,682  | 58,582        | 50.27%           | 14,100    | 48.35%           |
| Household income <sup>a</sup>               |         |               |                  |           |                  |
| Total (N)                                   | 140,925 | 112,740       |                  | 28,185    |                  |
| Median (IQR)                                |         | 13            | (9,16)           | 13        | (9,15)           |
| Infant feeding practices                    |         |               |                  |           |                  |
| Breast feeding                              | 67,937  | 53,464        | 45.88%           | 14,473    | 49.63%           |
| Bottle or mixed feeding                     | 77,722  | 63,045        | 54.10%           | 14,677    | 50.33%           |
| Unfavorable nutritional status <sup>b</sup> |         |               |                  |           |                  |
| Total (N)                                   | 133,069 | 106,101       |                  | 26,968    |                  |
| Median (IQR)                                |         | 0.22          | (0.16, 0.33)     | 0.25      | (0.16, 0.35)     |
| Parental safety awareness <sup>c</sup>      |         |               |                  |           |                  |
| Total (N)                                   | 145,679 | 116,526       |                  | 29,153    |                  |
| Median (IQR)                                |         | 0.2           | (0.2,0.4)        | 0.2       | (0.2, 0.4)       |
| Systemic corticosteroid prescription        |         |               |                  |           |                  |
| Total (N)                                   | 145,704 | 116,542       |                  | 29,162    |                  |
| Median (IQR)                                |         | 12            | (3.00, 31.00)    | 18        | (6.00, 42.00)    |
| Antihistamine prescription                  |         |               |                  |           |                  |
| Total (N)                                   | 145,704 | 116,542       |                  | 29,162    |                  |
| Median (IQR)                                |         | 222           | (110.00, 379.00) | 255       | (127.00, 432.00) |
| Methylphenidate prescription                |         |               |                  |           |                  |
| Total (N)                                   | 145,704 | 116,542       |                  | 29,162    |                  |
| Median (IQR)                                |         | 0             | (0,0)            | 0         |                  |

Abbreviation: AD, atopic dermatitis.

<sup>a</sup>Classified by quintiles (range: 1–5), with a higher score indicating lower income.

<sup>b</sup>Range: 0–6, with a higher score indicating poorer nutritional status.

<sup>c</sup>Range: 0–5, with a higher score indicating less parental safety awareness.

association between infantile feeding practices and the risk of fracture events (aOR: 1.08, 95% CI: 1.05–1.10). Infantile feeding practices were also one of the mediating factors but the mediation effect was weak, accounting for 1.0% (95% CI: 0.6–1.4) of the excess risk (Figure 2).

Lower weights at birth and during 4–6 months of age, lower household income, exclusively breastfeeding during 4–6 months of age, unfavorable parental safety awareness were related to increased fracture rates, but the association was not significant, and thus did not function as mediating factors (Table 4).

In additional mediation analysis in the subgroup of bones that were more easily affected by accidental injury (Subgroup A), the

mediation effect was consistent and corticosteroid prescription the largest mediating factor accounting for 28.8% (95% CI: 19.2%–50.0%) followed by antihistamine prescription accounting for 21.0% (95% CI: 13.5%–37.0%) (Table S11).

## 4 | DISCUSSION

We investigated the association of AD with fracture events in children and the mediating factors by examination of children with and without AD in a large-scale, population-based nationwide pediatric cohort

**TABLE 3** Propensity score-matched adjusted relative risk and pre-specified analysis of fracture in children with AD relative to controls

|                                    | Matched cohort (N = 145,704) <sup>a</sup> |                       | Relative risk (95% CI) <sup>c</sup> |
|------------------------------------|-------------------------------------------|-----------------------|-------------------------------------|
|                                    | Events, N (%)                             |                       |                                     |
| Main outcomes                      | Control group (n = 116,542) <sup>b</sup>  | AD group (n = 29,542) |                                     |
| Fracture of any bone               | 24,698 (21.2)                             | 6652 (22.8)           | 1.08 (1.05, 1.10)*                  |
| Fracture with splint application   | 14,973 (12.9)                             | 4033 (13.8)           | 1.08 (1.04, 1.11)*                  |
| Prespecified analysis : Subgroup 1 | Control group (n = 116,542) <sup>b</sup>  | AD group (n = 29,542) | Relative risk (95% CI) <sup>c</sup> |
| Skull and facial bones             | 8531 (7.3)                                | 2330 (8.0)            | 1.09 (1.04, 1.14)*                  |
| Trunk including vertebrae          | 202 (0.2)                                 | 80 (0.3)              | 1.58 (1.22, 2.05)*                  |
| Proximal limbs                     | 4597 (3.9)                                | 1131 (3.9)            | 0.98 (0.92, 1.05)                   |
| Distal limb                        | 13,957 (12.0)                             | 3875 (13.3)           | 1.11 (1.07, 1.15)*                  |
| Prespecified analysis : Subgroup 2 | Control group (n = 116,542) <sup>b</sup>  | AD group (n = 29,542) | Relative risk (95% CI) <sup>c</sup> |
| Head and neck                      | 8533 (7.3)                                | 2334 (8.0)            | 1.09 (1.05, 1.14)*                  |
| Trunk                              | 8531 (7.3)                                | 2330 (8.0)            | 1.09 (1.04, 1.14)*                  |
| Upper extremity                    | 11,900 (10.2)                             | 3174 (10.9)           | 1.07 (1.03, 1.11)                   |
| Lower extremity                    | 6,61 (5.7)                                | 1890 (6.5)            | 1.13 (1.08, 1.19)                   |

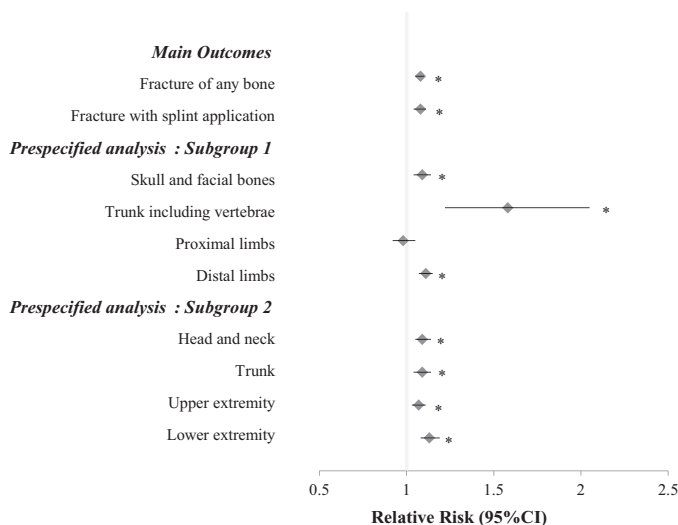
Abbreviation: AD, atopic dermatitis.

<sup>a</sup>Propensity score matching (1:4) was performed to reduce bias for selection of the comparison group using the Mahalanobis algorithm with a caliper of 0.01 and multivariable logistic regression with covariates as defined in Tables S4 and S5. The cohort included children who were born between January 1, 2008, and December 31, 2009, and participated in the first round and at least one of the fourth to seventh rounds of the national health-screening program.

<sup>b</sup>Reference group.

<sup>c</sup>Risk ratio (95% CI) was determined using modified Poisson regression with a log-link function.

\* $p < .001$ .



| Potential Mediating Factors                 | % Mediation (95%CI) <sup>a</sup> |
|---------------------------------------------|----------------------------------|
| Birth weight                                | -0.9 (-4.1–0.0)                  |
| Wt for age at 4–6 months <sup>b</sup>       | 0.35 (-2.05–3)                   |
| Birth residence                             | -0.2 (-0.7–0.0)                  |
| Household income quintile <sup>c</sup>      | -0.2 (-0.7–0.0)                  |
| Infantile feeding practices                 | 2.5 (1.1–4.0)                    |
| Unfavorable nutritional status <sup>d</sup> | 1.0 (-3.5–7.0)                   |
| Parental safety awareness <sup>e</sup>      | 0.1 (-0.8–1.0)                   |
| Systemic corticosteroid prescription        | 28.6 (19.2–50.0)                 |
| Antihistamine prescription                  | 19.6 (13.6–31.0)                 |
| Methylphenidate prescription                | 0.0 (-0.3–0.1)                   |

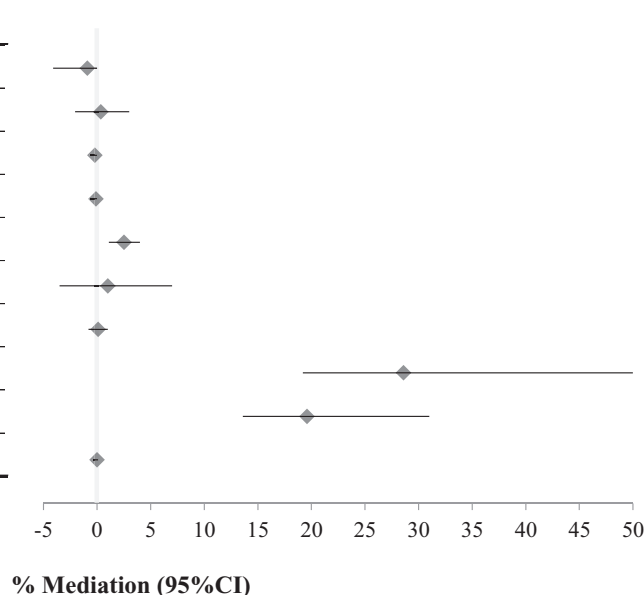


**FIGURE 2** Strength of different risk factors in mediating the association of AD with fracture. <sup>a</sup>Fully adjusted for birth year, certain conditions originating during the perinatal period, physical examination results at 4–6 months old, clinical conditions with possible confounding effects (Table S6), date of first AD diagnosis, and first recorded fracture diagnosis. <sup>b</sup>Percentage of weight-for-age from the Korean national growth charts for children and adolescents.<sup>15</sup> <sup>c</sup>Classified by quintiles (range: 1–5) with higher score indicating lower income. <sup>d</sup>Range: 0–6, with higher score indicating poorer nutritional status. <sup>e</sup>Range: 0–5, with higher score indicating less parental safety awareness

from Korea (n = 353,040). Boys and girls with AD had increased risk of fracture compared to those without AD, and the two largest mediating factors were use of corticosteroids and antihistamines.

Systemic corticosteroids are often used for management of AD, but these drugs are associated with many adverse effects, including reduced bone mineral density.<sup>17</sup> Previous research also reported an

TABLE 4 Mediating effects of different risk factors on the association of AD with fracture

|                                             | Sample size   |          | Birth year and sex adjusted least-squared mean (95% CI) <sup>a</sup> |                        | Difference between control and AD groups | Adjusted odds ratio <sup>b</sup> | Adjusted incidence proportion (95% CI)     |                                             | Absolute risk difference in incidence (95% CI) |
|---------------------------------------------|---------------|----------|----------------------------------------------------------------------|------------------------|------------------------------------------|----------------------------------|--------------------------------------------|---------------------------------------------|------------------------------------------------|
|                                             | Control group | AD group | Controls                                                             | AD group               |                                          |                                  | Factor absent or 25th percentile of factor | Factor present or 75th percentile of factor |                                                |
| Birth weight                                | 116,542       | 29,162   | 0.505 (0.501, 0.510)                                                 | 0.496 (0.487, 0.505)   | -0.009 (-0.020, 0.001)                   | 1.09 (0.91, 1.31)                | 21.0 (20.5, 21.5)                          | 22.5 (22.0, 23.0)                           | 1.5 (0.8, 2.1)                                 |
| Weight for age at 4–6 months <sup>d</sup>   | 116,490       | 29,152   | 0.497 (0.494, 0.501)                                                 | 0.494 (0.486, 0.501)   | -0.004 (-0.012, 0.005)                   | 1.07 (1.03, 1.12)                | 20.3 (19.8, 20.7)                          | 23.5 (23.1, 24.0)                           | 3.3 (2.7, 3.9)                                 |
| Birth residence                             | 115,500       | 28,890   | 0.502 (0.500, 0.505)                                                 | 0.489 (0.484, 0.495)   | -0.013 (-0.020, -0.007)                  | 1.01 (0.98, 1.03)                | 21.9 (21.6, 22.2)                          | 21.7 (21.4, 22.0)                           | -0.2 (-0.6, 0.2)                               |
| Household income <sup>f</sup>               | 112,740       | 28,185   | 0.507 (0.504, 0.510)                                                 | 0.500 (0.495, 0.506)   | -0.007 (-0.013, -0.000)                  | 1.03 (0.99, 1.05)                | 21.6 (21.3, 22.0)                          | 22.0 (21.7, 22.3)                           | 0.4 (-0.1, 0.8)                                |
| Infant feeding practice                     | 116,509       | 29,150   | 0.460 (0.457, 0.463)                                                 | 0.497 (0.491, 0.503)   | 0.037 (0.031, 0.044)                     | 1.08 (1.05, 1.10)                | 21.4 (21.1, 21.6)                          | 22.4 (22.1, 22.7)                           | 1.0 (0.6, 1.4)                                 |
| Unfavorable nutritional status <sup>g</sup> | 116,526       | 29,153   | 0.490 (0.485, 0.495)                                                 | 0.534 (0.525, 0.544)   | 0.044 (0.033, 0.055)                     | 1.01 (0.97, 1.05)                | 21.6 (21.1, 22.1)                          | 21.5 (21.0, 22.0)                           | -0.2 (-0.8, 0.6)                               |
| Parental safety awareness <sup>h</sup>      | 116,361       | 29,109   | 0.481 (0.476, 0.485)                                                 | 0.470 (0.461 to 0.480) | -0.010 (-0.021, -0.001)                  | 0.99 (0.95, 1.03)                | 21.7 (21.2, 22.2)                          | 22.0 (21.5, 22.5)                           | 0.3 (-0.4, 1.0)                                |
| Systemic corticosteroid prescription        | 116,542       | 29,162   | 0.471 (0.467, 0.475)                                                 | 0.617 (0.609, 0.625)   | 0.145 (0.137, 0.154)                     | 1.20 (1.15, 1.25)                | 20.4 (19.9, 20.8)                          | 23.5 (23.1, 23.9)                           | 3.1 (2.5, 3.7)                                 |
| Antihistamine prescription                  | 116,542       | 29,162   | 0.480 (0.476, 0.485)                                                 | 0.573 (0.565, 0.581)   | 0.092 (0.083, 0.101)                     | 1.30 (1.23, 1.37)                | 20.1 (19.7, 20.5)                          | 23.6 (23.1, 24.0)                           | 3.4 (2.8, 4.0)                                 |
| Methylphenidate prescription                | 115,817       | 28,926   | 0.003 (0.002 to 0.004)                                               | 0.004 (0.003 to 0.005) | 0.001 (0.000, 0.002)                     | 0.85 (0.66, 1.08)                | 21.8 (21.6, 22.0)                          | 22.9 (19.2, 26.7)                           | 1.1 (-2.6, 4.9)                                |

Abbreviation: AD, atopic dermatitis.

<sup>a</sup>For dichotomous variables, data were scored as 0 for “no” and 1 for “yes.”

<sup>b</sup>Adjusted for birth year, certain conditions originating during the perinatal period, physical examination results at 4–6 months old, clinical conditions with possible confounding effects (Table S6), date of first AD diagnosis, and first recorded fracture diagnosis. For example, data on infantile feeding practice were available for 116,500 individuals without AD and 29,150 individuals with AD. The birth year-adjusted least-squares mean excluding breastfeeding was 46.0 for individuals without AD (95% CI: 45.7, 46.3) and 49.7 for individuals with AD (95% CI: 49.1, 50.3), which differed by 3.7 (95% CI: 3.1, 3.4). The odds of developing fracture during follow-up was 1.08-times greater for those who were exclusively breastfed relative to those who were not; 22.4% (95% CI: 22.1, 22.7) of those who were exclusively breastfed developed fracture, and 21.4% (95% CI: 21.1, 21.6) of those who were not developed fracture, a difference of 1.0% (95% CI: 0.6, 1.4).

<sup>c</sup>Expressed for a 1-SD difference in a continuous predictor.<sup>d</sup>Weight-for-age calculated from the Korean national growth charts for children and adolescents.<sup>15</sup><sup>e</sup>Expressed as the difference in a dichotomous predictor.<sup>f</sup>Classified by quintiles (range: 1–5), with higher score indicating lower income.<sup>g</sup>Range: 0–6, with higher score indicating poorer nutritional status.<sup>h</sup>Range: 0–5, with higher score indicating less parental safety awareness.

association between moderate-to-severe AD and decreased bone density in children.<sup>17</sup> Studies of children and adults found that corticosteroid use was associated with musculoskeletal injuries including fracture.<sup>17,18</sup> Studies of adults reported that AD was significantly associated with low bone density,<sup>19,20</sup> which can lead to major fracture.<sup>21,22</sup> However, osteoporotic fracture rarely occurs in young age and researchers have documented that clinical risk factors are more important than bone density in childhood fracture.<sup>14</sup> These findings imply that increased fracture risks might be related to clinical risk factors related to AD, rather than decreased bone density such as in adults. We also found that risk between children with AD and controls were insignificant for bones prone to fracture when bone density decreased. The mediation effect of systemic corticosteroid prescription therefore might be related to the severity of AD rather than bone density.<sup>23</sup>

We also found that antihistamine use was a significant mediating factor. This might be because of the sedative effects of certain antihistamines, known to have negative effects on mood, alertness, and cognitive functions.<sup>24</sup> The Global Allergy and Asthma European Network task force issued a scientific statement stating that antihistamine use in infants and young children might result in unwanted side effects, such as accidents, suicide, and cardiotoxicity.<sup>25</sup> Previous studies of children documented that sedation from antihistamine use could possibly affect their performance and learning.<sup>26,27</sup>

Furthermore, the mediation effect of antihistamine might possibly be linked with sleep at night, which could lead to non-accidental injuries. However, when we additionally investigated the fracture rates in parts of bone that are closely related to non-accidental injury, the result was insignificant.

The greatest strength of this study is that we performed a systematic assessment of risk factors for fracture in a large population of children. This study had several limitations. The individuals in our study were aged 71 months or younger, so the generalizability of our findings to older children is uncertain. In addition, because this was an observational study there may have been measurement error or misclassification of the potential mediating factors, which could possibly lead to underestimation of the effects of the mediators. For example, since we used a large administrative data provided by the national health insurance service, we were not able to assess the histories or mechanisms of each fracture cases.

In summary, we found evidence supporting that childhood AD is related to higher fracture rates in children. Mediation analysis to compare fractures in children with and without AD exhibited that systemic use of corticosteroids and antihistamines are the leading mediating factors. Infant feeding type at the age of 4 to 6 months had weaker effects.

## CONFLICTS OF INTEREST

There was no conflict of interest relevant to this article.

## AUTHOR CONTRIBUTION

**Eun Kyo Ha:** Writing – original draft (lead); Writing – review & editing (lead). **Ju Hee Kim:** Funding acquisition (equal); Investigation (equal);

Resources (equal); Writing – review & editing (equal). **Ji Hee Kwak:** Investigation (supporting); Methodology (supporting). **Soonchul Lee:** Investigation (supporting); Supervision (supporting); Validation (supporting). **Hye Ryeong Cha:** Data curation (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Validation (supporting). **Eun Hee Chung:** Funding acquisition (lead); Investigation (supporting); Methodology (supporting); Supervision (supporting); Validation (supporting). **Man Yong Han:** Conceptualization (lead); Data curation (equal); Formal analysis (equal); Supervision (equal); Validation (equal); Visualization (lead).

## PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13712>.

## DATA AVAILABILITY STATEMENT

Data described in the manuscript, codebook, and analytic code will be made available upon request pending application and approval.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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