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Association of fracture incidence in children with the development of food allergy: A Korean nationwide birth cohort study

Running head: Food allergy and fracture in children

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Dr SWL and DKY 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*: RK, SWL, YHS, JIS, and DKY; *Acquisition, analysis, or interpretation of data*: SWL, YHS, JIS, and DKY; *Drafting of the manuscript*: RK, SWL, YHS, JIS, and DKY; *Critical revision of the manuscript for important intellectual content*: all authors; *Statistical analysis*: SWL, YHS, JIS, and DKY; *Study supervision*: SWL, DKY. DKY is a 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

Globally, the prevalence of food allergy (FA) in children is increasing, and FA can induce fatal anaphylaxis, which affects morbidity and mortality.[1,2] Children with FAs are more likely to have food neophobia, which may lead to severe vitamin D deficiency and osteoporosis. Although some studies suggested milk avoidance specifically, which leads young children to be prone to bone fracture[3], no studies have investigated whether children with FAs are at increased risk of fracture, and hence there is a need to determine the direct association between FA and fracture incidence during childhood. We hypothesized that FAs are linked with an increased risk of fracture. Therefore, the relationship between FA diagnosis and fracture incidence in approximately two million children was examined in this representative large-scale nationwide birth cohort from the National Health Insurance Service in South Korea.

1,778,588 Korean infants born between 2008 and 2015 who completed the first national health examination for infants were followed up until December 2019. The study protocol was approved by the Institutional Review Board of Sejong University (SJU-HR-E-2021-001) and Seoul National University (E-2108-134-1246). In addition, the ethics committee waived the requirement to obtain written informed consent due to the use of routinely collected health data.

FAs were determined by using ICD-10 codes (Z91.0 and T78.0) with more than 2 claims within 1 year.[4] Children who experienced food-induced anaphylaxis (T78.0) were categorized as moderate to severe FAs. Otherwise, children have mild FAs diagnosed with ICD-10 code of Z91.0: personal history of allergy.

To balance the probability of patients with and without FA, we performed an exposure-driven propensity score matching (PSM) driven by a logistic regression model with adjustment.[5] A greedy nearest-neighbor algorithm was implemented to pair participants in two groups in an 1:3 ratio. Cox proportional hazards regression model with hazard ratios (HRs) and 95% confidence intervals (CIs) was applied to estimate adjusted hazard ratios (aHRs) by using SPSS (version 25.0; IBM Corp, Armonk, NY, USA), SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) and R software (version 3.1.1; R Foundation, Vienna, Austria).[6] A p-value of $p < 0.05$ was considered statistically significant.

A total of 1,778,588 children (boy n=920,342 [51.8%]) were analyzed (Table S1). After a 1:3 exposure-driven PSM, there were 6,578 (15.7%) incident fractures and no major imbalances in the baseline covariates when evaluated using standardized mean differences (SMDs) between both the groups (Table S1; FA [n=10,442] vs. control [n=31,326]; all SMDs <0.001). In this matched cohort, children with FAs had an 11% greater likelihood of developing overall fracture after full adjustment for confounders (Table 1; fracture incidence rate [1,000 person-years]: 41.84 for FAs vs. 36.60 for control). The risk of fracture increased with increasing FA severity (fracture incidence rate [1,000 person-years]: 36.60 for control vs. 40.63 for mild FA vs. 48.61 for moderate to severe FA). This corresponded to 1 extra fracture per 205 FA children followed for one year. There was a 9% increase in the risk of overall fracture in children with mild FAs (aHR, 1.09; 95% CI: 1.03–1.16) and a 21% increase in those with moderate to severe FAs (aHR, 1.21; 95% CI: 1.08–1.35). We also analyzed to determine whether the age at the first FA diagnosis influenced fracture risk. The earlier the development of FA, the higher the risk of fractures (aHR for the first FA diagnosis at <2 years, 1.19 [95% CI: 1.08–1.31]; aHR for the first FA diagnosis at 2–4 years, 1.09 [95% CI: 1.01–1.19]; and aHR for the first FA diagnosis at ≥5 years, 1.14 [95% CI: 1.04–1.26]).

Furthermore, we found that increasing the number of hospital visits due to FAs increases the risk of fracture (aHR for the number of hospital visits due to FAs <3 times, 1.07 [95% CI: 0.99–1.16] and aHR for the number of hospital visits due to FAs ≥3 times, 1.13 [95% CI: 1.06–1.22]).

The fracture risk following the FA diagnosis was greater at 0–1 year of age after the FA diagnosis (aHR, 1.24; 95% CI: 1.07–1.44), and this risk remained and persisted until 5 years (Figure 1). We observed a similar effect and patterns in a fracture site in Figure 1 and Table S2: head (aHR, 1.14; 95% CI: 1.01–1.30); upper limb (aHR, 1.08; 95% CI: 1.01–1.17); lower limb (aHR, 1.17; 95% CI: 1.05–1.29); spine (aHR, 0.51; 95% CI: 0.11–2.30); and others (aHR, 0.95; 95% CI: 0.54–1.65). In the stratification analyses, similar patterns of fracture risk were found according to sex, calendar year of birth, region of residence, birth season, and height. However, no breastfeeding attenuated the risk of overall fracture (aHR for breastfeeding, 1.16; 95% CI: 1.08–1.24 vs. aHR for no breastfeeding, 0.99; 95% CI: 0.89–1.10). The results from the entire cohort were consistent with our main results from the matched cohort (Data not shown; Tables S3–6 are accessible only to reviewers).

A few immunological mechanisms may explain the association of FA with fracture risk. First, the complexity between the immune-mediated pathological mechanism of FAs with osteoimmunology (i.e., Th17 polarization) has provided the cross-regulation of the immune system and bone, which comprises various cell types, signaling pathways, cytokines, and chemokines.[7] Second, children with FAs (especially cow milk allergy) may not intake enough calcium or vitamin D that prevents aggravation of their condition, which may lead to malnutrition and the development of osteoporosis.[8]

There are several limitations to this study. First, our study does not have information on whether children with FAs undergo disease remission or whether children with disease remission have a decreased risk of fracture during childhood. Also, we could not account for some potential confounding factors or mediators (i.e., vitamin D level, malnourishment, sleep quality, psychological status and physical activity status) because our claims-based data were not collected systematically. In spite of these limitations, this study includes the nationwide birth cohort design minimizing sampling bias, a large sample size of 1.78 million children, several strict exposure-driven PSM approaches to reduce immortal bias, and adjustments for various potential confounding factors including breastfeeding history. Furthermore, our study is the first to determine the relationship between FA and fractures to the best of our knowledge.

In summary, FAs are a significant risk factor for fractures in children, although it should also be noted that the absolute risk of fractures in children is low. Our data suggested 1 extra fracture per 205 FA children and year. Risks increased with severity and early onset of FA and hospital visits due to FA, and were particularly high during the first year after FA diagnosis.

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. Dr Abuabara is a consultant for TARGET RWE. The other authors declare no competing interests.

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Figure 1. Estimated aHRs for the likelihood of incident fracture after FA diagnosis. Blue dots indicate aHR for diagnosis time periods; red dots indicate aHR for anatomical sites; Whiskers represent 95% CIs. CI, confidence interval; FA, food allergy; aHR, adjusted hazard ratio.

Table 1. Cox proportional hazards model to determine the relationship of food allergy with a subsequent overall bone fracture in each 1:3 propensity score-matched cohort.

					Hazard ratio (95% CI)		
Parameter	N (%)	Fracture events	Person-years	Fracture incidence rate*	Crude	Model 1§	Model 2‡
Food allergy							
None	31,326(75.0%)	4778	130,559	36.60	1.0 (reference)	1.0 (reference)	1.0 (reference)
Food allergy	10,442(25.0%)	1800	43,026	41.84	**1.14 (1.08 to 1.21)**	**1.14 (1.08 to 1.21)**	**1.11 (1.05 to 1.17)**
Severity of food allergy							
None	31,326(75.0%)	4778	130,559	36.60	1.0 (reference)	1.0 (reference)	1.0 (reference)
Mild food allergy	8605(20.6%)	1485	36,547	40.63	**1.11 (1.05 to 1.18)**	**1.12 (1.06 to 1.19)**	**1.09 (1.03 to 1.16)**
Moderate to severe food allergy	1837(4.4%)	315	6480	48.61	**1.30 (1.16 to 1.46)**	**1.25 (1.11 to 1.40)**	**1.21 (1.08 to 1.35)**
First diagnostic age of food allergy, years							

Comparator**	10,414(24.9%)	2384	60,320	39.52	1.0 (reference)	1.0 (reference)	1.0 (reference)
<2	3951(9.5%)	995	22,288	44.64	**1.22 (1.11 to 1.34)**	**1.22 (1.11 to 1.34)**	**1.19 (1.08 to 1.31)**
Comparator**	12,911(30.9%)	1897	53,944	35.17	1.0 (reference)	1.0 (reference)	1.0 (reference)
2-4	3879(9.3%)	619	15,673	39.49	**1.12 (1.02 to 1.23)**	**1.12 (1.02 to 1.22)**	**1.09 (1.01 to 1.19)**
Comparator**	8001(19.2%)	497	16,295	30.50	1.0 (reference)	1.0 (reference)	1.0 (reference)
≥5	2612(6.2%)	186	5065	36.72	**1.17 (1.06 to 1.29)**	**1.17 (1.06 to 1.29)**	**1.14 (1.04 to 1.26)**
Number hospital visits due to food allergy							
None	31,326 (75.0%)	4778	130,559	36.59	1.0 (reference)	1.0 (reference)	1.0 (reference)
< 3	4,425 (10.6%)	702	18,729	37.48	**1.03 (0.95 to 1.12)**	**1.06 (0.98 to 1.15)**	**1.07 (0.99 to 1.16)**
≥ 3	6,017 (14.4%)	1098	24297	45.19	**1.23 (1.15 to 1.31)**	**1.20 (1.12 to 1.28)**	**1.13 (1.06 to 1.22)**

Abbreviation: CI, confidence interval.

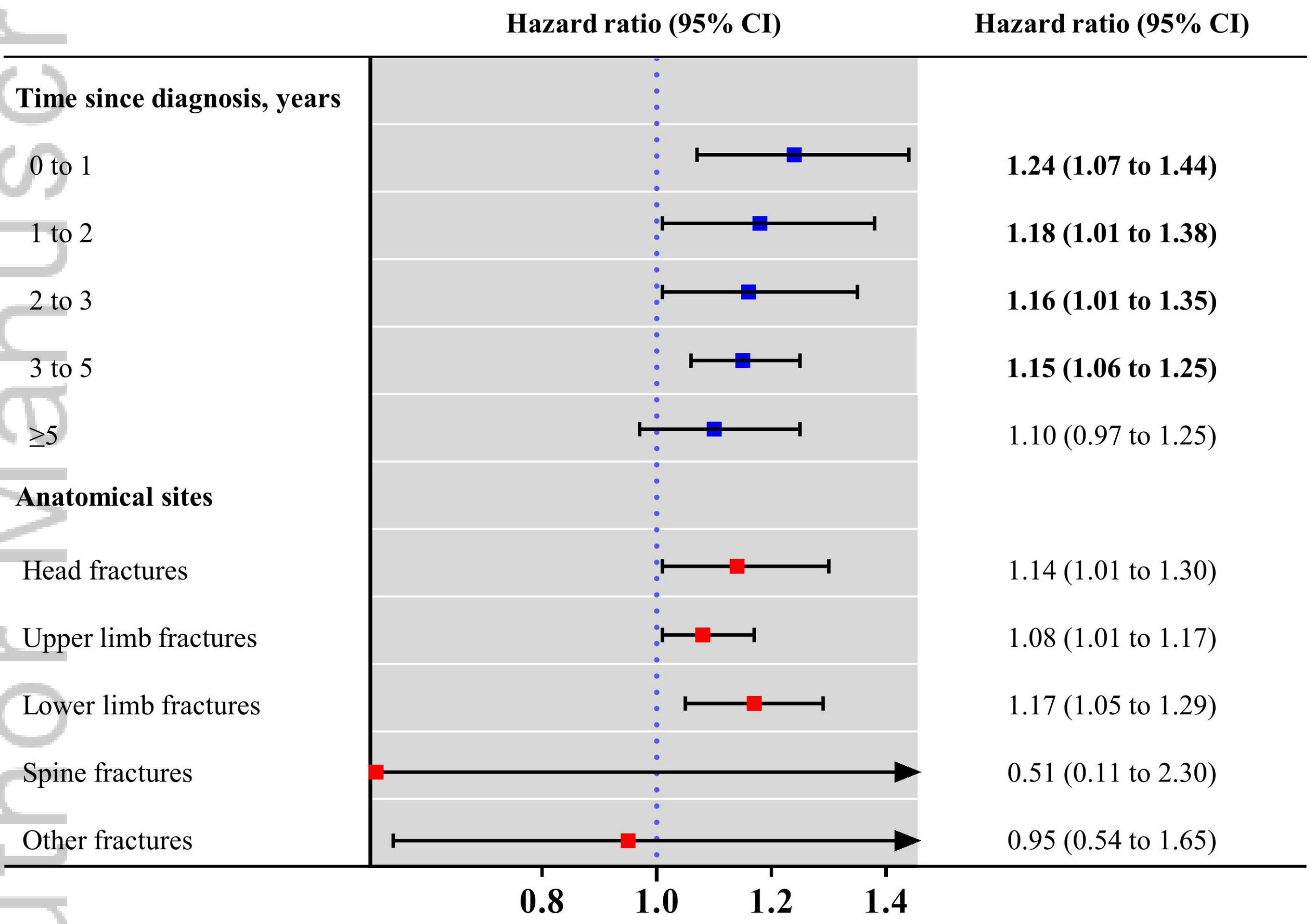
*Fracture incidence rate is expressed per 1,000 person-years

[§]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, and long-term use of systemic corticosteroids.

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

Numbers in bold correspond to significant differences (P <0.05).



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