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## Original Article

# Early-onset-early-resolving atopic dermatitis does not increase the risk of development of allergic diseases at 3 Years old



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### KEYWORDS

Atopic dermatitis;  
Atopic march;  
Parental atopy history

**Background:** Epidemiological findings showed the increased risk of allergic rhinitis (AR) and asthma in the children with preceding atopic dermatitis (AD). In this study, we aimed to observe the development of allergic diseases in infantile AD patients.

**Methods:** We followed up the prospective observational cohort enrolling two-to four-month-old exclusively breastfed infants. The presence of physician-diagnosed asthma, AR and AD at age 3 was recorded with the laboratory tests for atopic sensitization.

**Results:** Fifty infantile AD patients and 48 healthy controls were enrolled. The sex, age and parental atopy history were not significantly different between the two groups. At age 3, 21 (42%) patients had persistent AD in the infantile AD group while only 2 (4.2%) patients had newly diagnosed AD in the control group ( $p < 0.001$ ). The early-onset-early-resolving AD (subsides before age 2) did not increase the risk of AR and asthma development, and the sensitization to allergens. However, the early-onset-persistent AD (persists after age 2) increased the risk of AR development and sensitization to inhalant allergens (adjusted odds ratio 2.83, 7.07, respectively). The parental atopy status was associated with any allergic disease at age 3 ( $p = 0.020$ ). The maternal atopy history was the significant factor associated with AD, AR and eosinophilia at age 3 ( $p = 0.004, 0.014, 0.031$ , respectively).

**Conclusion:** The early-onset-early-resolving AD was not associated with allergic diseases development at age 3. The parental atopy history and early-onset-persistent AD might be the risk factors for development of allergic diseases at age 3.

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## Introduction

Atopic dermatitis (AD) is one of the most common pediatric inflammatory skin disorders, with a prevalence worldwide of approximately 10%–21%.<sup>1</sup> In Taiwan, the International Study of Asthma and Allergies in Childhood (ISAAC) survey by questionnaires in 2001–2002 showed that the AD prevalence (recurrent rash at typical eczema distribution) is around 6% in children at 6–8 years old.<sup>2,3</sup> The concept of “atopy” (derived from the Greek *atopia*, meaning “placelessness”) was introduced by Coca and Cooke in 1923 to describe the phenomena of allergic hypersensitivity.<sup>4</sup> Atopy is characterized by exaggerated immune responses to allergic stimuli and high IgE that can lead to clinical disease at a variety of anatomic sites. Atopic individuals are predisposed to the development of allergies, such as AD, allergic rhinitis (AR), and asthma.<sup>5</sup> Atopic march, originally defined 15 years ago, is the development of AD in infancy and subsequent food allergy (FA), AR, and asthma in later childhood.<sup>6</sup> This concept was based on the epidemiological findings of the increased risk of AR and asthma in the children with preceding AD, and a murine model that epicutaneous sensitization with ovalbumin (OVA) and development of dermatitis enables the later development of aerosolized OVA induced airway hyperreactivity and eosinophilia in the bronchoalveolar lavage fluid without the need for prior airway sensitization.<sup>1,7</sup>

We have launched the prospective observational cohort study which enrolled two- to four-month-old exclusively breastfed infants with AD or healthy controls in National Taiwan University Hospital (NTUH) from September 2015 to June 2016. We found that vitamin D levels in breast milk (BM) for exclusively breastfed infants were negatively associated with objective SCORing Atopic Dermatitis index (objSCORAD). Lower vitamin D levels in BM might be a risk factor for infantile AD.<sup>8</sup> In this study, we aimed to follow these infants till 3 years old and find out the association of allergic diseases development and AD in the early infancy.

## Methods

### Study design and participants

This was a prospective observational cohort study which enrolled two- to four-month-old exclusively breastfed infants in NTUH from September 2015 to June 2016. Infants with major diseases such as autoimmune disorders, malignancy, primary immunodeficiency disorders, and congenital anomalies were excluded. The study was approved by the Research Ethics Committee of NTUH (NTUH-REC No.: 201406029RINC) and informed consent was obtained from all participants' guardians.

Exclusive breastfeeding was defined as the infant receiving only BM without the addition of infant formula and supplementary food. The subjects were divided into two groups according to the presence of physician-diagnosed AD: AD group and control group. The diagnosis of AD was based on the typical morphology and atopic distribution from the criteria established by Hanifin and Rajka.<sup>9</sup> The severity of AD was assessed by the same allergist by using objSCORAD.<sup>10</sup>

All baseline characteristics such as sex, age, ethnicity, and parental atopy history were obtained. The atopy history included ever asthma, AR, and/or AD. The parental atopy status depends on the number of parents with atopy history.

All of the study subjects were followed up by telephone contacts at 3 years of age. The presence of physician-diagnosed asthma, AR and AD at age 3 was recorded. AD was subsided when symptom-free days were more than 12 months. Infantile AD status was divided into 3 groups: no AD (never had AD), early-onset-early-resolving AD (infantile AD subsided in the first 2 years of life) and early-onset-persistent AD (infantile AD persisted after 2 years old). In the analysis regarding infantile AD status, 2 patients who developed AD after 2 years old in the control group were excluded.

### Laboratory tests

All of the study subjects were invited to have optional blood tests for MAST<sup>TM</sup> (Optigen® allergen-specific IgE assay, Hitachi, CA, USA), total IgE (ImmunoCAP® assay, Thermo Fisher Scientific Inc., Denmark), eosinophil count, and Vit D levels (LIAISON®, Diasorin, Italian) at 3 years old. Eosinophilia was defined as eosinophil  $\geq 500$  cells/ $\mu$ L; abnormal IgE level was defined as IgE  $\geq 100$  kU<sub>A</sub>/L; sensitization to allergens was defined as allergen-specific IgE  $\geq 2+$  (66LU<sub>s</sub>); and Vit D sufficiency was defined as serum 25-(OH) D  $\geq 30$  ng/mL.

### Statistical analysis

The data of continuous variables were shown as mean  $\pm$  SEM (interquartile range) as appropriate, while the categorical variables were shown as number (percentage) of patients as appropriate. We compared the categorical variables between groups by Pearson's chi-squared test. We compared the continuous variables between the two groups by the independent *t*-test if the data followed a normal distribution or by the Mann–Whitney U test if the data was not normally distributed. Stepwise multiple regression analysis was used to determine the significant factors for the development of AR, asthma, AD, and atopic sensitization at age 3. Logistic regression was used to investigate the association between infantile AD status and asthma, AR, and atopic sensitization. The adjusted odds ratio (OR) included adjustment for the potential confounders: sex and parental atopy history. A *p* value  $< 0.05$  was considered significant. All statistical analyses were performed with IBM SPSS statistical software (version 20.0.0, IBM Corp., NY, USA).

## Results

### Characteristics and laboratory tests of study population

One hundred and nine exclusively breastfed infants were enrolled: 57 healthy controls and 52 infants with physician-diagnosed AD. There were 9 controls and 2 patients lost to

follow up at age 3. The final in analysis children were 48 healthy controls and 50 infantile AD patients. Table 1 shows the characteristics of AD infants and healthy controls. At enrollment, the mean ages were  $3.63 \pm 0.13$  and  $3.25 \pm 0.15$  months old in the infantile AD and control groups, respectively. The mean objSCORAD was  $21.51 \pm 1.72$  in infantile AD group at enrollment. The percentages of male infants in the infantile AD and control groups were 50.0% and 47.9%, respectively. No significant difference was found between the two groups with regard to age, sex and parental atopy history. Most of the ethnicity of study subjects were Han Chinese, except one father in the control group and one parents in the infantile AD group were Austronesians. In the infantile AD group, there were 21 (42%) patients had persistent AD at age 3. On the other hand, there were only 2 (4.2%) patients had newly diagnosed AD after 2 years of age in the control group ( $p < 0.001$ ). There were more allergic diseases at age 3 in infantile AD group compared to control groups (74% vs 43.8%,  $p = 0.002$ ).

The laboratory tests were surveyed optionally at age 3. There were 23 (46.0%) infantile AD patients and 21 (43.8%) healthy controls receiving blood tests. The eosinophil percentage, total eosinophil count, IgE levels were not significantly different between infantile AD and control groups. However, there were more infantile AD patients sensitized to inhalant allergens compared to control group (73.9% vs

42.9%,  $p = 0.036$ ). Although serum vitamin D levels were not different in both groups, the proportion of vitamin D sufficiency subjects were significantly higher in control group than infantile AD group (47.6% vs 13%,  $p = 0.012$ ).

### Allergic diseases at 3 years old

The characteristics of allergic diseases at age 3, such as AD, AR and asthma, were shown in Table 2. The infantile AD was significantly associated with AD at age 3 ( $p < 0.001$ ). AR was significantly associated with AD and asthma ( $p = 0.004$  and  $0.002$ , respectively). There were no significant differences for the sex and parental atopy history between allergic and non-allergic groups, except maternal atopy history was higher in AR patients ( $p = 0.009$ ). The objSCORAD at infancy was higher in AD patients compared to non-AD patients at age 3 ( $22.89 \pm 3.05$ ,  $7.32 \pm 1.32$ , respectively,  $p < 0.001$ ). Interestingly, the objSCORAD at age 3 was not only significantly higher in AD patients, but was also significantly higher in AR patients when compared to non-AR patients ( $3.74 \pm 0.96$ ,  $0.81 \pm 0.34$ , respectively,  $p = 0.004$ ).

We also analyzed the association between allergic diseases and parental atopy status (Table 3). We found that there was no difference in infantile AD group according to the number of allergic parents. However, there were

**Table 1** Characteristics and laboratory tests<sup>a</sup> of atopic dermatitis infants and healthy controls.

|                                                     | Infantile AD (n = 50)          | Control (n = 48)               | p value          |
|-----------------------------------------------------|--------------------------------|--------------------------------|------------------|
| Male Sex                                            | 25 (50.0%)                     | 23 (47.9%)                     | 0.837            |
| Age at enrollment (months)                          | $3.63 \pm 0.13$ (2.56–4.29)    | $3.25 \pm 0.15$ (2.17–4.26)    | 0.219            |
| Ethnicity:                                          |                                |                                |                  |
| Han Chinese                                         | 49                             | 47                             | 0.368            |
| Han Chinese – Austronesian                          | 0                              | 1                              |                  |
| Austronesian                                        | 1                              | 0                              |                  |
| Paternal atopy history                              | 33 (66.0%)                     | 26 (54.2%)                     | 0.232            |
| Maternal atopy history                              | 27 (54.0%)                     | 22 (45.8%)                     | 0.419            |
| Parental atopy history                              | 42 (84.0%)                     | 39 (81.3%)                     | 0.719            |
| ObjSCORAD at enrollment                             | $21.51 \pm 1.72$ (11.3–29.5)   | 0                              | <b>&lt;0.001</b> |
| AD at age 3                                         | 21 (42.0%)                     | 2 (4.2%)                       | <b>&lt;0.001</b> |
| AR at age 3                                         | 28 (56.0%)                     | 19 (39.6%)                     | 0.104            |
| Asthma at age 3                                     | 13 (26.0%)                     | 9 (18.8%)                      | 0.390            |
| Any allergic disease at age 3                       | 37 (74.0%)                     | 21 (43.8%)                     | <b>0.002</b>     |
| ObjSCORAD at age 3                                  | $3.48 \pm 0.76$ (0.0–4.58)     | $0.90 \pm 0.64$ (0.0–0.0)      | <b>&lt;0.001</b> |
| Eosinophil percentage (%)                           | $4.25 \pm 0.60$ (1.90–5.30)    | $3.71 \pm 0.65$ (1.15–6.05)    | 0.358            |
| Total eosinophil count (cells/ $\mu$ L)             | $352.9 \pm 47.1$ (195.0–505.7) | $294.6 \pm 49.7$ (97.4–448.3)  | 0.318            |
| Eosinophilia <sup>b</sup>                           | 6 (26.1%)                      | 5 (23.8%)                      | 0.862            |
| IgE (kU <sub>A</sub> /L)                            | $332.5 \pm 78.5$ (53.7–586.0)  | $266.7 \pm 83.8$ (26.4–309.0)  | 0.307            |
| Abnormal IgE level ( $\geq 100$ kU <sub>A</sub> /L) | 16 (69.6%)                     | 11 (52.4%)                     | 0.242            |
| Sensitization to mite                               | 16 (69.6%)                     | 9 (42.9%)                      | 0.074            |
| Sensitization to inhalant allergens                 | 17 (73.9%)                     | 9 (42.9%)                      | <b>0.036</b>     |
| Sensitization to food allergens                     | 8 (34.8%)                      | 6 (28.6%)                      | 0.659            |
| 25-(OH) D (ng/mL)                                   | $24.97 \pm 1.59$ (20.30–27.30) | $28.91 \pm 1.79$ (22.55–35.25) | 0.142            |
| Vitamin D sufficiency                               | 3 (13.0%)                      | 10 (47.6%)                     | <b>0.012</b>     |

Data shown are mean  $\pm$  SEM (interquartile range) or number (%) of patients as appropriate.

AD, atopic dermatitis; objSCORAD, objective SCORing Atopic Dermatitis index; AR, allergic rhinitis.

A p value  $< 0.05$  was considered significant, which was showed in bold.

<sup>a</sup> There were 23 (46.0%) infantile AD patients and 21 (43.8%) healthy controls receiving laboratory tests at age 3.

<sup>b</sup> Eosinophilia was defined as eosinophil  $\geq 500$  cells/ $\mu$ L.

**Table 2** Characteristics of different allergic diseases at age 3.

|                        | AD                          |                         | p value          | AR                       |                          | p value      | Asthma                    |                           | p value      |
|------------------------|-----------------------------|-------------------------|------------------|--------------------------|--------------------------|--------------|---------------------------|---------------------------|--------------|
|                        | Yes (n = 23)                | No (n = 75)             |                  | Yes (n = 47)             | No (n = 51)              |              | Yes (n = 22)              | No (n = 76)               |              |
| Infantile AD           | 21 (91.3%)                  | 2 (2.7%)                | <b>&lt;0.001</b> | 28 (59.6%)               | 19 (37.3%)               | 0.104        | 13 (59.1%)                | 9 (11.8%)                 | 0.390        |
| AD at age 3            |                             |                         |                  | 17 (36.2%)               | 6 (11.8%)                | <b>0.004</b> | 6 (27.3%)                 | 16 (21.1%)                | 0.633        |
| AR at age 3            | 17 (73.9%)                  | 6 (8.0%)                | <b>0.004</b>     |                          |                          |              | 17 (77.3%)                | 5 (6.6%)                  | <b>0.002</b> |
| Asthma at age 3        | 6 (26.1%)                   | 17 (22.7%)              | 0.633            | 17 (36.2%)               | 5 (9.8%)                 | <b>0.002</b> |                           |                           |              |
| Male Sex               | 11 (47.8%)                  | 37 (49.3%)              | 0.899            | 23 (48.9%)               | 25 (49.0%)               | 0.993        | 8 (36.4%)                 | 40 (52.6%)                | 0.179        |
| Paternal atopy history | 15 (65.2%)                  | 44 (58.7%)              | 0.574            | 27 (57.4%)               | 32 (62.7%)               | 0.592        | 15 (68.2%)                | 44 (57.9%)                | 0.385        |
| Maternal atopy history | 15 (65.2%)                  | 34 (45.3%)              | 0.095            | 30 (63.8%)               | 19 (37.3%)               | <b>0.009</b> | 15 (68.2%)                | 34 (44.7%)                | 0.053        |
| Parental atopy history | 20 (87.0%)                  | 61 (81.3%)              | 0.533            | 40 (85.1%)               | 41 (80.4%)               | 0.538        | 19 (86.4%)                | 62 (81.6%)                | 0.602        |
| ObjSCORAD at infancy   | 22.89 ± 3.05<br>(11.3–32.0) | 7.32 ± 1.32<br>(0–11.7) | <b>&lt;0.001</b> | 11.04 ± 1.81<br>(0–19.1) | 10.92 ± 2.13<br>(0–22.5) | 0.505        | 14.32 ± 3.24<br>(0–27.08) | 10.01 ± 1.54<br>(0–17.53) | 0.228        |
| ObjSCORAD at age 3     | 9.44 ± 1.37                 | 0                       | <b>&lt;0.001</b> | 3.74 ± 0.96              | 0.81 ± 0.34              | <b>0.004</b> | 4.02 ± 1.68               | 1.69 ± 0.44               | 0.432        |

Data shown are mean ± SEM (interquartile range) or number (%) of patients as appropriate.

AD, atopic dermatitis; AR, allergic rhinitis; objSCORAD, objective SCORing Atopic Dermatitis index.

A p value < 0.05 was considered significant, which was showed in bold.

**Table 3** Prevalence of allergic diseases, according to parental atopy status.

|                               | Total (n = 98) | No allergy parents (n = 17) | Only 1 allergic parent (n = 54) | Two allergic parents (n = 27) | p value      |
|-------------------------------|----------------|-----------------------------|---------------------------------|-------------------------------|--------------|
| Infantile AD                  | 50 (51.0%)     | 8 (47.1%)                   | 24 (44.4%)                      | 18 (66.7%)                    | 0.158        |
| AD at age 3                   | 23 (23.5)      | 3 (17.6%)                   | 10 (18.5%)                      | 10 (37.0%)                    | 0.148        |
| AR at age 3                   | 47 (48.0%)     | 7 (41.2%)                   | 23 (42.6%)                      | 17 (63.0%)                    | 0.185        |
| Asthma at age 3               | 22 (22.4%)     | 3 (17.6%)                   | 8 (14.8%)                       | 11 (40.7%)                    | <b>0.027</b> |
| Any allergic disease at age 3 | 58 (59.2%)     | 8 (47.1%)                   | 28 (51.9%)                      | 22 (81.5%)                    | <b>0.020</b> |

Data shown are number (%) of patients.

AD, atopic dermatitis; AR, allergic rhinitis.

A p value < 0.05 was considered significant, which was showed in bold

significantly more asthma and any allergic diseases at age 3 in children born to both allergic parents ( $p = 0.027$  and  $0.020$ , respectively).

### Laboratory tests in allergic diseases at age 3

In [Table 4](#), the allergic diseases at age 3 were significantly correlated to atopic status. In AD, more patients had significantly eosinophilia, positive IgE, and sensitization to inhalant and food allergens ( $p = 0.019$ ,  $0.011$ ,  $0.007$ ,  $0.002$ , respectively). In AR, more patients had significantly eosinophilia and sensitization to inhalant allergens ( $p = 0.013$ ,  $<0.001$ , respectively), while significantly higher IgE levels were noted in the AR patients ( $p = 0.004$ ). Only eosinophilia was significantly different between asthma patients and non-asthma groups ( $p = 0.004$ ). Neither vitamin D level nor vitamin D sufficiency proportion

was different in patients and non-patients of AD, AR and asthma.

For the prevalence of atopy status ([Table 5](#)), more allergic diseases patients tend to have more eosinophilia, positive IgE, sensitization to mite and inhalant allergens ( $p = 0.002$ ,  $0.012$ ,  $0.004$ ,  $0.003$ , respectively), but there was no difference in sensitization to food allergens.

### Association between infantile AD status and allergic disease or atopy status

After excluding 2 patients who developed AD after 2 years old in the control group, the study subjects were grouped into 3: no AD (never had AD), early-onset-early-resolving AD (infantile AD subsides in the first 2 years of life) and early-onset-persistent AD (infantile AD persisted after 2 years old). There were 46 children in no AD group, 26 patients in early-onset-early resolving AD group and 24 patients in

**Table 4** Laboratory tests for different allergic diseases at age 3.

|                                                     | AD                                          |                                           | p value      | AR                                          |                                          | p value          | Asthma                                     |                                           | p value      |
|-----------------------------------------------------|---------------------------------------------|-------------------------------------------|--------------|---------------------------------------------|------------------------------------------|------------------|--------------------------------------------|-------------------------------------------|--------------|
|                                                     | Yes (n = 12)                                | No (n = 32)                               |              | Yes (n = 26)                                | No (n = 18)                              |                  | Yes (n = 16)                               | No (n = 28)                               |              |
| Eosinophil percentage (%)                           | 4.95 ± 0.64<br>(3.58–6.18)                  | 3.63 ± 0.55<br>(1.40–5.03)                | 0.054        | 4.95 ± 0.64<br>(2.48–6.30)                  | 3.63 ± 0.55<br>(1.00–3.35)               | 0.054            | 5.58 ± 0.92<br>(2.03–8.40)                 | 3.09 ± 0.36<br>(1.75–4.18)                | <b>0.021</b> |
| Total eosinophil count (cells/ $\mu$ L)             | 435.7 ± 67.9<br>(217.1–660.2)               | 283.6 ± 37.4<br>(118.3–384.9)             | 0.051        | 435.7 ± 67.9<br>(231.5–586.5)               | 283.6 ± 37.4<br>(94.9–210.0)             | 0.051            | 457.0 ± 67.4<br>(186.0–742.3)              | 249.6 ± 29.7<br>(141.9–354.6)             | <b>0.014</b> |
| Eosinophilia<br>IgE (kU <sub>A</sub> /L)            | 6 (50.0%)<br>534.2 ± 124.5<br>(176.3–800.0) | 5 (15.6%)<br>213.7 ± 56.5<br>(25.1–285.3) | <b>0.019</b> | 10 (38.5%)<br>534.2 ± 124.5<br>(50.3–606.5) | 1 (5.6%)<br>213.7 ± 56.5<br>(25.3–165.0) | <b>0.013</b>     | 8 (50.0%)<br>452.8 ± 110.1<br>(53.3–769.3) | 3 (10.7%)<br>214.4 ± 58.9<br>(30.5–264.3) | <b>0.004</b> |
| Abnormal IgE level ( $\geq 100$ kU <sub>A</sub> /L) | 11 (91.7%)                                  | 16 (50.0%)                                | <b>0.011</b> | 19 (73.1%)                                  | 8 (44.4%)                                | 0.055            | 12 (75.0%)                                 | 15 (53.6%)                                | 0.160        |
| Sensitization to mite                               | 11 (91.7%)                                  | 14 (43.8%)                                | <b>0.004</b> | 20 (76.9%)                                  | 5 (27.8%)                                | <b>0.001</b>     | 11 (68.8%)                                 | 14 (50.0%)                                | 0.227        |
| Sensitization to inhalant allergens                 | 11 (91.7%)                                  | 15 (46.9%)                                | <b>0.007</b> | 21 (80.8%)                                  | 5 (27.8%)                                | <b>&lt;0.001</b> | 11 (68.8%)                                 | 15 (53.6%)                                | 0.325        |
| Sensitization to food allergens                     | 8 (66.7%)                                   | 6 (18.8%)                                 | <b>0.002</b> | 10 (38.5%)                                  | 4 (22.2%)                                | 0.256            | 5 (31.3%)                                  | 9 (32.1%)                                 | 0.951        |
| 25-(OH) D (ng/mL)                                   | 25.09 ± 2.03<br>(18.20–29.48)               | 27.51 ± 1.49<br>(20.93–34.50)             | 0.382        | 26.77 ± 1.74<br>(20.03–32.70)               | 26.96 ± 1.65<br>(25.38–33.18)            | 0.940            | 26.14 ± 1.99<br>(19.13–31.01)              | 27.25 ± 1.56<br>(20.80–33.50)             | 0.687        |
| Vitamin D sufficiency                               | 3 (25.0%)                                   | 10 (31.3%)                                | 0.686        | 8 (30.8%)                                   | 5 (27.8%)                                | 0.831            | 4 (25.0%)                                  | 9 (32.1%)                                 | 0.617        |

Data shown are mean  $\pm$  SEM (interquartile range) or number (%) of patients as appropriate.

AD, atopic dermatitis; AR, allergic rhinitis.

A p value &lt; 0.05 was considered significant, which was showed in bold

early-onset-persistent AD group. Neither early-onset-early-resolving AD nor early-onset-persistent AD increased the risk for asthma. However, early-onset-persistent AD increased the risk of AR. Besides, early-onset-persistent AD increased the risk of sensitization to mite or inhalant allergens (Table 6).

After multiple regression by a conditional forward method, the factors that are significantly associated with AD at age 3 are the infantile AD status and maternal atopy history ( $p < 0.001$ ,  $= 0.004$ , respectively) after adjusting for sex and paternal atopy history; the only factor that is significantly associated with AR and eosinophilia at age 3 is maternal atopy history ( $p = 0.014$ ,  $0.031$ , respectively) after adjusting for sex, paternal atopy history and infantile AD status; the factor that is significantly associated with sensitization to food allergens at age 3 is the infantile AD status ( $p = 0.026$ ) after adjusting for sex, maternal and paternal atopy history.

## Discussion

The atopic march referred to the progression from AD to the manifestation of FA, AR and asthma in later childhood. AD tends to be the initial manifestation of the atopic march, and sensitization through the skin is likely an important initial step in the development of other allergic diseases.<sup>5</sup> Development of these allergic diseases is strongly influenced by the following two factors: skin dysfunction caused by filaggrin mutations and development of colonization of microflora in early infancy.<sup>11</sup> Filaggrin (FLG) mutations predisposing to asthma, AR and allergic sensitization, only in the presence of AD, strongly support the role of FLG in the pathogenesis of AD and in subsequent progression of the atopic march.<sup>6</sup> Several studies have shown that development of colonization of microflora in early infancy might prevent the development of allergic disease or FA.<sup>6</sup> Therefore, allergen exposure through skin barrier defect in early infancy and an imbalance of microflora might be necessary for development of atopic march.

The Tucson Children's Respiratory Study of an unselected birth cohort showed that eczema at the age of 1.5 years was associated with persistent wheezing at 6 years (OR 2.4).<sup>12</sup> A whole population-based birth cohort study from the Isle of Wight reported that eczema at 4 years increased the risk of asthma at 10 years (OR 2.15).<sup>13</sup> The German Multicenter Allergy Study (MAS)<sup>14</sup> and the Melbourne Atopic Cohort Study (MACS)<sup>15</sup> showed that eczema in the first 2 years of life was related to an increased risk of current wheeze at 6–7 years, but this association disappeared after adjusting for early wheeze and early-life sensitization. The authors argued that eczema was not an independent risk factor for subsequent asthma, and attributed the association to confounding by early wheeze and sensitization that co-manifested with early-life eczema.<sup>6</sup> The Canadian Healthy Infant Longitudinal Development (CHILD) Study found that AD diagnosed in infancy significantly increased the risk of being diagnosed with AR (RR: 3.66), FA (RR: 7.22) and asthma (RR: 2.63) at 5 years old as well as any allergic sensitization (RR: 2.92) at 5 years old.<sup>16</sup> In our study, the eczema subsided in the

**Table 5** Prevalence of atopy status according to allergic disease numbers.

|                                                        | Total<br>(n = 44) | No allergic<br>diseases (n = 12) | Only 1 allergic<br>disease (n = 15) | Only 2 allergic<br>diseases (n = 12) | Three allergic<br>diseases (n = 5) | p value      |
|--------------------------------------------------------|-------------------|----------------------------------|-------------------------------------|--------------------------------------|------------------------------------|--------------|
| Eosinophilia                                           | 11 (25.0%)        | 0 (0.0%)                         | 2 (13.3%)                           | 5 (41.7%)                            | 4 (80.0%)                          | <b>0.002</b> |
| Abnormal IgE level<br>( $\geq 100$ kU <sub>A</sub> /L) | 27 (61.4%)        | 3 (25.0%)                        | 11 (73.3%)                          | 8 (66.7%)                            | 5 (100.0%)                         | <b>0.012</b> |
| Sensitization to<br>mite                               | 25 (56.8%)        | 2 (16.7%)                        | 9 (60.0%)                           | 9 (75.0%)                            | 5 (100.0%)                         | <b>0.004</b> |
| Sensitization to<br>inhalant<br>allergens              | 26 (59.1%)        | 2 (16.7%)                        | 10 (66.7%)                          | 9 (75.0%)                            | 5 (100.0%)                         | <b>0.003</b> |
| Sensitization to<br>food allergens                     | 14 (31.8%)        | 2 (16.7%)                        | 4 (26.7%)                           | 5 (66.7%)                            | 3 (60.0%)                          | 0.282        |

Data shown are number (%) of patients.

A p value &lt; 0.05 was considered significant, which was showed in bold

**Table 6** Association between infantile atopic dermatitis status and allergic diseases or atopic sensitization.<sup>a</sup>

|                                                     | No.   | Crude OR (95% CI)        | Adjusted <sup>b</sup> OR (95% CI) |
|-----------------------------------------------------|-------|--------------------------|-----------------------------------|
| AR                                                  |       |                          |                                   |
| No AD                                               | 17/46 | Ref                      | Ref                               |
| Early-onset-early-resolving AD <sup>c</sup>         | 13/26 | 1.71 (0.64–4.52)         | 1.69 (0.64–4.50)                  |
| Early-onset-persistent AD <sup>d</sup>              | 15/24 | <b>2.84 (1.03–7.89)</b>  | <b>2.83 (1.02–7.88)</b>           |
| Asthma                                              |       |                          |                                   |
| No AD                                               | 8/46  | Ref                      | Ref                               |
| Early-onset-early-resolving AD                      | 8/26  | 2.11 (0.68–6.53)         | 2.26 (0.72–7.15)                  |
| Early-onset-persistent AD                           | 5/24  | 1.25 (0.36–4.34)         | 1.19 (0.34–4.20)                  |
| Eosinophilia                                        |       |                          |                                   |
| No AD                                               | 3/19  | Ref                      | Ref                               |
| Early-onset-early-resolving AD                      | 2/11  | 1.19 (0.17–8.47)         | 1.49 (0.19–11.87)                 |
| Early-onset-persistent AD                           | 4/12  | 2.67 (0.48–14.90)        | 3.43 (0.56–21.22)                 |
| Abnormal IgE level ( $\geq 100$ kU <sub>A</sub> /L) |       |                          |                                   |
| No AD                                               | 9/19  | Ref                      | Ref                               |
| Early-onset-early-resolving AD                      | 7/11  | 1.94 (0.42–8.92)         | 2.17 (0.43–10.97)                 |
| Early-onset-persistent AD                           | 9/12  | 3.33 (0.68–16.30)        | 3.88 (0.75–20.15)                 |
| Sensitization to mite                               |       |                          |                                   |
| No AD                                               | 7/19  | Ref                      | Ref                               |
| Early-onset-early-resolving AD                      | 7/11  | 3.00 (0.64–14.02)        | 3.57 (0.65–19.66)                 |
| Early-onset-persistent AD                           | 9/12  | <b>5.14 (1.03–25.60)</b> | <b>7.47 (1.26–44.30)</b>          |
| Sensitization to<br>inhalant allergens              |       |                          |                                   |
| No AD                                               | 7/19  | Ref                      | Ref                               |
| Early-onset-early-resolving AD                      | 8/11  | 4.57 (0.90–23.14)        | 4.76 (0.83–27.22)                 |
| Early-onset-persistent AD                           | 9/12  | <b>5.14 (1.03–25.60)</b> | <b>7.07 (1.23–40.60)</b>          |
| Sensitization to food allergens                     |       |                          |                                   |
| No AD                                               | 5/19  | Ref                      | Ref                               |
| Early-onset-early-resolving AD                      | 1/11  | 0.28 (0.03–2.78)         | 0.15 (0.01–1.85)                  |
| Early-onset-persistent AD                           | 7/12  | 3.92 (0.84–18.22)        | 4.66 (0.87–24.91)                 |

AD, atopic dermatitis; AR, allergic rhinitis; Ref, reference odds.

<sup>a</sup> Exclude 2 patients who developed AD after 2 years old.<sup>b</sup> Adjusted for parental atopy history and sex.<sup>c</sup> Early-onset-early-resolving AD denotes infantile AD subsides in the first 2 years of life.<sup>d</sup> Early-onset-persistent AD denotes infantile AD persists after age 2.

first 2 years of life (early-onset-early-resolving AD) did not increase the risk of being diagnosed with AR, AD and asthma at age 3, which was similar to MAS and MACS study.

Only a small subset of children in the general population (approximately 3%) appear to follow the complete course of atopic march. Even in high-risk cohorts, a stepwise

progression from AD to FA, asthma, and AR is not common.<sup>17</sup> AD and early allergic sensitization are linked to specific high-atopy phenotypes of childhood asthma, which might be of special clinical significance in terms of lower lung function and increased asthma morbidity.<sup>18,19</sup> A European cohort study noted that early-onset-persistent AD increased the risk of asthma (aOR 2.87; 95% CI 1.31–6.315), AR (4.04; 1.82–8.955) and sensitization to inhalant allergens (3.36; 1.78–6.355) at age 6.<sup>20</sup> The factors that are strongly associated with asthma development are atopic endotype of AD (increased IgE and Th2 predominant), early-onset AD (before 2 years old), moderate to severe AD, persistent AD (lasting longer than 3 years) and gene mutations (e.g., FLG, thymic stromal lymphopoietin [TSLP]).<sup>21</sup> Early-onset-persistent AD, multisensitization to allergens, and familial atopy are risk factors for the classical atopic march or development of multiple comorbidities.<sup>17</sup> In our study, the infantile AD was only associated with AD at age 3, but not AR and asthma (Table 1). In sub-analysis of these patients, we found that only early-onset-persistent AD increased the risk of AR development and sensitization to inhalant allergens at age 3 (Table 6). After multiple regression, the infantile AD status was associated with AD and sensitization to food allergens at age 3, which might imply that skin barrier defects in patients with AD increase the risk of epicutaneous sensitization to food allergens.<sup>17</sup>

Depending on epidemiologic studies, the most common forms of AD onset is very early onset of AD (between 3 months and 2 years, 60–80%), then adult onset (20%) and childhood onset (10%).<sup>22</sup> Between 10% and 25% of children in developed countries present with AD within the first year of life. In two UK-based population study, one found that 11.2% of infants between 6 and 12 months had AD and in the other 24.4% of infants had AD by 3 months.<sup>23,24</sup> A substantial portion of these patients can go into complete remission before age of 2 years. Another portion, which is estimated roughly at 40%, continues to have the disease over a longer period of time and could represent the population with the highest risk for the atopic march.<sup>22</sup> Early-onset-early-resolving AD accounts for 12.9% in ALSPAC,<sup>25</sup> and 15.4% in PIAMA cohort,<sup>26</sup> which has a favorable prognosis and is only very weakly associated with asthma in later life.<sup>27</sup> Two classes of persistent disease (early-onset-persistent and early-onset-late-resolving) were most strongly associated with an AD-genetic risk score as well as personal and parental history of atopic disease. Importantly, these classes display strong comorbidity with asthma.<sup>27</sup> Our study also showed that early-onset-early-resolving AD did not increase the risk of AR and asthma development, while early-onset-persistent AD increased the risk of AR development.

The prevalence survey of allergic diseases in Taiwan in 2001–2002 by the ISAAC questionnaires showed that 19.4% had rhinitis only, 4.6% had eczema only, 4.7% had asthma only at age 6–8. Interestingly, 5.2% had asthma and rhinitis, 3.2% had rhinitis and eczema, 0.5% had asthma and eczema, and 1.9% had 3 allergic diseases.<sup>2</sup> In our study, AR at age 3 had significantly more comorbidities such as AD and asthma (Table 2), possibly due to the high prevalence of AR. Epidemiological evidence demonstrates that AD, AR and asthma are temporally associated to each other and may be causally related.<sup>21</sup> For the atopy status,

eosinophilia was significantly higher in the AD, AR and asthma patients, while IgE level and sensitization to either mite or inhalant allergens were significantly higher in the AD and AR patients only. Not surprisingly, the more allergic diseases the patients had, the more eosinophilia, positive IgE and sensitization to inhalant allergens they had (Table 5). However, the sensitization to food allergens were only significantly associated with infantile AD status by multiple regression.

Children whose parents are both atopic are 5.35 times more likely to develop early-onset-persistent AD, a phenotype associated with the atopic march.<sup>20</sup> The genetic trait, such as FLG and TSLP, were related to atopic march. The statistical relationships indicate that FLG mutations predispose individuals for AD, which then predisposes for asthma. TSLP variations are independently affiliated with asthma and AD, it is possible that this is a linking genetic factor between these diseases.<sup>21</sup> In our study, parental atopy status was correlated to any allergic disease at age 3, especially asthma. The maternal atopy history was the significant factor associated with AD, AR and eosinophilia. Therefore, family history especially maternal atopy history was important in the development of allergic diseases.

Our previous study showed that the vitamin D levels in BM was significantly lower in the infantile AD group than in the control group.<sup>8</sup> However, the serum vitamin D levels at age 3 were not different in both groups. The correlation of sun exposure time and serum vitamin D levels was not significant (data not shown). Although there were more children with vitamin D sufficiency in the control group, it could be due to other factors such as diet or effective sun exposure than the vitamin D levels in BM. Vitamin D has immunomodulatory effects on allergen-induced inflammatory pathways in a variety of immune cells, including B cells, T cells, dendritic cells and macrophages.<sup>28</sup> In 616 Costa Rican children with asthma aged 6–14 years, 28% of the children had insufficient 25-(OH) D levels, and 25-(OH) D levels were significantly inversely associated with total IgE and eosinophil count.<sup>29</sup> Low levels of vitamin D appear to be inversely correlated with AD severity.<sup>28</sup> However, there were no difference of serum vitamin D levels in AD, asthma and AR at age 3 in the present study. The small sample size warrant further larger scale study to define the role of vitamin D in allergic diseases and atopic march.

The limitations of our study are small sample size, short observational period, no extensive blood tests and no genetic trait detected. Some allergic diseases developed later than age 3, so the prevalence of allergic diseases may be higher when we prolong the observational period. The optional blood test in around 45% of children may lead to bias in this study. Besides, we did not check the genetic trait such as FLG gene, which is the important gene mutation in AD. In the future, we will follow these children for longer period, and persuade them for blood tests when they grow older and do the genetic study. It will give us more comprehensive data about the association of AD in early infancy and atopic march. In addition, all our study subjects were exclusively breastfed infants at enrollment. The results in our study might not be applied to formula-fed or partially breastfed infants.

In conclusion, the prospective observational cohort study showed that AD in the early infancy was significantly

associated with AD at age 3. However, only the early-onset-persistent AD increased the risk of AR development and sensitization to inhalant allergens. The early-onset-early-resolving AD did not increase the risk of AR and asthma development, and the sensitization to allergens. The parental allergic status was associated with any allergic disease at age 3. The maternal atopy history was the significant factor associated with AD, AR and eosinophilia. Therefore, the parental atopy history and early-onset-persistent AD might be the risk factors for development of allergic diseases at age 3.

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## Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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