

# Increased risk of idiopathic nephrotic syndrome in children with atopic dermatitis

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## Abstract

**Background** Clinical and immunological studies have consistently shown a relationship between atopic diathesis and idiopathic nephrotic syndrome (INS). However, no large population cohort study has yet to demonstrate the nature of the relationship between these disorders.

**Methods** Claims data from a random selection of children representing half of the insured population in Taiwan were examined. During the period from 1998 to 2007, we identified 192,295 children aged <18 years with newly diagnosed atopic dermatitis (AD) and 769,169 frequency-matched controls. Incidence of INS and hazard ratios (HRs) were calculated.

**Results** The AD cohort had a 2-fold higher overall incidence of INS than the non-AD cohort [7.20 vs. 3.60 per 100,000

person-years, respectively; 95 % confidence interval (CI) 1.50–2.66]. The HR for INS increased with age and was higher among females. The HR for INS was also higher in AD children with more medical visits per year, ranging from 0.94 for those having  $\leq 3$  visits to 38.6 for those having >6 visits (trend test  $P < 0.0001$ ). In particular, the risk of INS clearly increased during the initial 5 years after AD onset.

**Conclusions** Children with AD have a greater incidence and risk of developing INS and this risk increases with AD severity.

**Keywords** Atopy · Atopic dermatitis · IgE · Incidence rate · Idiopathic nephrotic syndrome · Minimal change disease

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## Introduction

Idiopathic nephrotic syndrome (INS) is among the most common chronic kidney diseases in children [1], and its association with atopic diathesis (AD) has been recognized for more than 50 years [2–11]. Elevated serum immunoglobulin E (IgE) levels, a key step in the allergic inflammatory cascade, are also commonly found in children with INS [9, 12–17]. Although major research efforts have been made to further our understanding of the clinical and immunological features of allergic diseases in INS, the nature of the relationship between AD and INS remains unclear [11–17].

AD is a chronic and relapsing inflammatory skin disease which usually presents with early onset and precedes other allergic disorders in early childhood [18, 19]. We conducted a retrospective population-based cohort analysis to investigate the incidence and risk of INS in children with AD as index disease with the aim of improving our understanding of the development of INS in children with AD.

## Materials and methods

### Data sources

All data used in this retrospective cohort study were recorded in the National Health Insurance (NHI) Research Database of Taiwan. This database is maintained by the National Health

Research Institutes of Taiwan. Taiwan's NHI program is a single-payer social insurance plan which covers almost all citizens with modest cost sharing (<http://www.nhi.gov.tw/english/index.aspx>) [20, 21]. For our analysis, we obtained the NHI files on children (age <18 years) generated from 2000 to 2008. The dataset consisted of a randomly selected sample representing half of all insured children in Taiwan. Detailed information about the dataset was presented in a previous study [20]. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used to define diagnostic disease codes.

### Study subjects

We constructed a retrospective cohort in the study. A total of 192,295 patients (age <18 years) newly diagnosed with AD (ICD-9-CM code 691) between 2000 and 2007 were identified as the AD cohort. The baseline was set as the date of AD diagnosis. For each child with AD, we randomly selected four non-AD children matched by sex, age (within a 1-year interval), urbanization of residence area, parental occupation, and baseline year. We used the method of 1:4 matching to increase the statistical power and to control potential confounding. To improve diagnostic accuracy and avoid any overestimation of prevalence, only those individuals having at least three consecutive corresponding diagnoses were designated as having AD and INS. Renal biopsy is usually not indicated at the first presentation of childhood INS, and empirical steroid treatment

**Table 1** Sociodemographic characteristics of the children with atopic dermatitis (AD) and of the non-AD controls

| Sociodemographic characteristics | Non-AD controls ( <i>n</i> =769,179) |        | AD cohort ( <i>n</i> =192,295) |        | <i>P</i> value |
|----------------------------------|--------------------------------------|--------|--------------------------------|--------|----------------|
|                                  | <i>n</i>                             | %      | <i>n</i>                       | %      |                |
| Age (years), mean ± SD           | 3.31                                 | ±4.39  | 3.24                           | ±4.42  | <0.0001        |
| Age (years) <sup>a</sup>         |                                      |        |                                |        | 0.99           |
| ≤2                               | 494,960                              | (64.4) | 123,740                        | (64.4) |                |
| 2–5                              | 87,276                               | (11.4) | 21,819                         | (11.4) |                |
| 5–12                             | 128,788                              | (16.7) | 32,197                         | (16.7) |                |
| >12                              | 58,155                               | (7.56) | 14,539                         | (7.56) |                |
| Sex                              |                                      |        |                                |        | 0.99           |
| Female                           | 358,984                              | (46.7) | 89,746                         | (46.7) |                |
| Male                             | 410,195                              | (53.3) | 102,549                        | (53.3) |                |
| Urbanization <sup>b</sup>        |                                      |        |                                |        | 0.99           |
| 1                                | 245,920                              | (32.0) | 61,480                         | (32.0) |                |
| 2                                | 227,007                              | (29.5) | 56,752                         | (29.5) |                |
| 3                                | 137,244                              | (17.8) | 34,311                         | (17.8) |                |
| 4                                | 159,008                              | (20.7) | 39,752                         | (20.7) |                |
| Occupation of parents            |                                      |        |                                |        | 0.99           |
| White collar                     | 485,836                              | (63.2) | 121,459                        | (63.2) |                |
| Blue collar                      | 169,128                              | (22.0) | 42,282                         | (22.0) |                |
| Others                           | 114,215                              | (14.9) | 28,554                         | (14.9) |                |

<sup>a</sup> *P* value determined using the chi-square test, with the exception of mean age ± standard deviation (SD), which was determined using the *t* test

<sup>b</sup> The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized

is often considered prior to kidney biopsy, as noted in our previous study [21]. As a result, the most common coding of children with INS in our dataset was unspecified pathologic lesion in kidney (ICD-9-CM code 581.9; 86.8 %), and not minimal change disease (MCD; ICD-9-CM code 581.3). Therefore, it is possible that most cases of MCD without histology confirmation were coded as 581.9. INS was diagnosed with ICD-9-CM codes 581.3 and 581.9. Patients with secondary nephrotic syndrome (NS) with ICD-9-CM code 581.8 were excluded from the study, as were patients with a history of INS before the baseline or for whom the information on age or sex was incomplete. Finally, the AD and the non-AD cohorts were followed up from 2000 until an INS event appeared or the study termination date of December 31, 2008 was reached; patients were censored when they were lost to follow-up or died.

### Statistical analysis

All data analyses were performed using the SAS software (version 9.2 for Windows; SAS Institute Inc., Cary, NC), with

the significance level set at 0.05 for a 2-tailed test. The Kaplan–Meier survival curve was plotted using R software (version 2.14.1; R Development Core Team, Vienna, Austria). The data analysis first compared the AD cohort with the non-AD cohort on the proportional distributions of socio-demographic status. The age-, gender-, urbanization level- and parental occupation-specific incidence densities of INS were estimated in both cohorts. The Cox proportional hazard regression model was used to assess the risk of developing INS associated with the AD cohort, compared with the non-AD cohort. The hazard ratio (HR) and 95 % confidence interval (CI) were calculated using the model. The Cox model was also used to estimate the HR of INS associated with the average frequency of medical visits by the AD cohort, compared with the non-AD cohort. We further assessed the role of AD duration by using time-dependent covariates ( $\leq 5$  and  $> 5$  years since AD diagnosis). We used the Kaplan–Meier method to estimate the cumulative incidence of INS and the log-rank test to examine the statistical significance of the differences between the two cohorts.

**Table 2** The incidence rate and hazard ratio of idiopathic nephrotic syndrome in children with atopic dermatitis (AD) and in non-AD controls, stratified by age, sex, urbanization of residential area, and occupation of parents

| Sociodemographic characteristics | Non-AD controls ( <i>n</i> =769,179) |              |      | AD cohort ( <i>n</i> =192,295)    |              |      | Age-adjusted HR (95 % CI) |
|----------------------------------|--------------------------------------|--------------|------|-----------------------------------|--------------|------|---------------------------|
|                                  | Nephrotic syndrome (no. of cases)    | Person-years | IR   | Nephrotic syndrome (no. of cases) | Person-years | IR   |                           |
| All                              | 141                                  | 391,4829     | 3.60 | 71                                | 98,5605      | 7.20 | 2.00 (1.50–2.66)***       |
| Age (years)                      |                                      |              |      |                                   |              |      |                           |
| ≤2                               | 97                                   | 2,397,055    | 4.05 | 42                                | 603,574      | 6.96 | 1.72 (1.20–2.47)**        |
| 2–5                              | 17                                   | 487,119      | 3.49 | 8                                 | 122,919      | 6.51 | 1.86 (0.80–4.32)          |
| 5–12                             | 25                                   | 721,813      | 3.46 | 15                                | 181,734      | 8.25 | 2.39 (1.26–4.53)**        |
| >12                              | 2                                    | 308,843      | 0.65 | 6                                 | 77,378       | 7.75 | 12.0 (2.42–59.4)**        |
| <i>P</i> for interaction         |                                      |              |      |                                   |              |      | 0.05                      |
| Sex                              |                                      |              |      |                                   |              |      |                           |
| Female                           | 41                                   | 1,830,115    | 2.24 | 26                                | 460,844      | 5.64 | 2.52 (1.54–4.12)***       |
| Male                             | 100                                  | 2,084,715    | 4.80 | 45                                | 524,761      | 8.58 | 1.78 (1.25–2.53)**        |
| Urbanization <sup>a</sup>        |                                      |              |      |                                   |              |      |                           |
| 1                                | 36                                   | 1,244,705    | 2.89 | 25                                | 314,049      | 7.96 | 2.75 (1.65–4.58)***       |
| 2                                | 42                                   | 1,153,494    | 3.64 | 18                                | 290,391      | 6.20 | 1.70 (0.98–2.94)          |
| 3                                | 31                                   | 704,071      | 4.40 | 11                                | 177,806      | 6.21 | 1.41 (0.71–2.81)          |
| 4                                | 32                                   | 812,559      | 3.94 | 17                                | 204,079      | 8.33 | 2.11 (1.17–3.80)*         |
| Occupation                       |                                      |              |      |                                   |              |      |                           |
| White collar                     | 91                                   | 2,537,163    | 3.59 | 43                                | 638,706      | 6.73 | 1.88 (1.31–2.70)***       |
| Blue collar                      | 37                                   | 908,411      | 4.07 | 14                                | 228,029      | 6.14 | 1.50 (0.81–2.78)          |
| Others                           | 13                                   | 469,254      | 2.77 | 14                                | 118,871      | 11.8 | 4.22 (1.98–8.98)***       |

\**P*<0.05, \*\**P*<0.01, \*\*\**P*<0.001

IR, Incidence rate per 100,000 person-years; HR, relative hazard ratio; CI, confidence interval

<sup>a</sup> Urbanization levels are described in the footnote to Table 1

## Results

We identified 192,295 AD patients eligible for the study and 769,179 patients in the non-AD cohort. The sociodemographic characteristics of the two cohorts are shown in Table 1. The mean age of children with AD and without AD was 3.24 [standard deviation (SD) 4.42] and 3.31 (SD 4.39), respectively. In the AD cohort, there were more boys (53.3 %), more patients living in urban areas (61.5 %), and more white-collar parents (63.2 %). There were no differences in age group, gender, urbanization of living areas, or parental occupation between the two cohorts.

The incidence of INS in both cohorts and the AD to non-AD HR of INS by sociodemographic status are presented in Table 2. Overall, the INS incidence was 2-fold greater in the AD cohort than in the non-AD cohort (7.20 vs. 3.60 per 100,000 person-years, respectively), with an adjusted HR of 2.00 (95 % CI 1.50–2.66). The incidence rate of INS was highest in the 5- to 12-year-old age group of the AD cohort and was higher for boys than for girls in both cohorts. The corresponding HR increased with age. Children aged >12 years had the highest age-adjusted HR for INS (HR 12; 95 % CI: 2.42–59.4) compared with the non-AD cohort. The sex- and urbanization-specific HR for the AD cohort compared with those of the non-AD cohort were both approximately 2–3.

The Kaplan–Meier analysis showed that the accumulated incidence rate of INS was significantly greater in the AD cohort (log-rank test  $P < 0.0001$ ; Fig. 1a) and greater in the children of the AD cohort with more AD-related medical visits (log-rank test  $P < 0.0001$ ; Fig. 1b). Table 3 shows the association between average frequency of medical visits due to AD and the development of INS. The average frequency of AD visits was estimated per year. Overall, the risk of INS increased with the number of medical visits and ranged from 0.94 (95 % CI 0.64–1.39) for those having  $\leq 3$  visits to 38.6 for those having >6 visits (trend test  $P < 0.0001$ ). As shown in Table 3, children with AD had a higher adjusted HR of 2.13 (95 % CI 1.58–2.88) for being diagnosed with INS within 5 years of diagnosis with AD. The adjusted HR decreased to 1.19 (95 % CI 0.48–2.95) after the 5-year follow-up.

## Discussion

This is the first population-based cohort study to investigate the incidence and risk of INS in children with AD compared with non-AD controls. Previous studies have extensively assessed the association between atopy and INS [2–11]. However, most of these studies were anecdotal reports or cross-sectional case–control studies with limited numbers of patients that found a high prevalence of AD in patients with INS but failed to demonstrate a causative role of atopy in INS

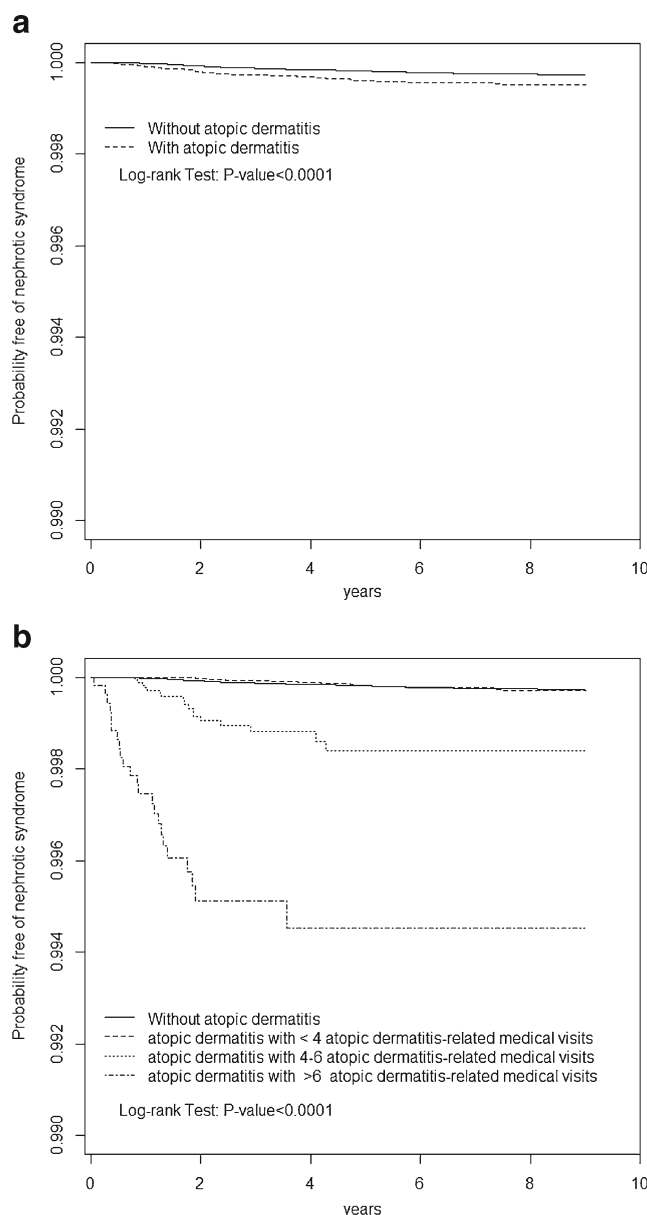


**Fig. 1** The accumulative incidence of idiopathic nephrotic syndrome. **a** In children with and without atopic dermatitis (AD), **b** in non-AD and AD children according to frequency of AD-related medical visits

[2–11]. Our large population cohort study supports the relationship between pre-existing AD and the subsequent risk for INS. This relationship was consistent in our cohort of children with AD across the strata of gender, age, urbanization of living area and parents' occupation. The relationship was strongest during the first 5 years after the onset of AD and correlated with the severity of AD, indicating a dose–effect relationship.

The annual incidence of NS in children in the USA and in Europe has been estimated to be 1–7 per 100,000 children [1, 22]. Our study revealed an annual incidence rate of 3.60 per 100,000 children in the non-AD cohort and a significantly increased incidence rate of 7.20 per 100,000 children in the AD cohort in Taiwan. In addition, the incidence rate and HR

**Table 3** The incidence rate and age-adjusted hazard ratio of idiopathic nephrotic syndrome in children with atopic dermatitis (AD) compared to the non-AD controls, stratified by frequency of AD-related annual medical visits and number of follow-up years

| Stratification variables                                  | Nephrotic syndrome (no. of cases) | Person-years | IR    | Age-adjusted HR (95 % CI) |
|-----------------------------------------------------------|-----------------------------------|--------------|-------|---------------------------|
| Frequency of AD-related annual medical visits (time/year) |                                   |              |       |                           |
| Non-AD controls                                           | 141                               | 3,914,829    | 3.60  | 1.00                      |
| ≤3                                                        | 31                                | 912,629      | 3.40  | 0.94 (0.64–1.39)          |
| 4–6                                                       | 17                                | 56,713       | 30.0  | 8.05 (4.86–13.3)***       |
| >6                                                        | 23                                | 16,262       | 141.4 | 38.6 (24.8–60.2)***       |
| <i>P</i> for trend                                        |                                   |              |       | <0.0001                   |
| Number of follow-up years <sup>a</sup>                    |                                   |              |       |                           |
| ≤5                                                        |                                   |              |       |                           |
| Non-AD controls                                           | 121                               | 3,111,846    | 3.89  | 1.00                      |
| AD cohort                                                 | 65                                | 782,364      | 8.31  | 2.13 (1.58–2.88)***       |
| >5                                                        |                                   |              |       |                           |
| Non-AD cohort                                             | 20                                | 802,982      | 2.49  | 1.00                      |
| AD children                                               | 6                                 | 203,241      | 2.95  | 1.19 (0.48–2.95)          |

\*\*\**P*<0.001<sup>a</sup> The median follow-up time is partitioned into two segments (≤5 vs. >5 years)

further increased in children who made more medical visits for AD, i.e., those with more serious or uncontrolled skin inflammation due to AD.

AD is a chronic or relapsing inflammatory skin disease that often precedes asthma and allergic disorders; as such, it represents the beginning of the atopic march [23]. Over 50 % of children with AD will develop asthma and/or allergic rhinitis [24]. The prevalence of AD in school-aged children in the USA has been reported to be 8.7–18 % [25] and has increased in the past three decades [23, 26]. Therefore, the AD cohort is an important model to investigate the impact of atopy on certain diseases. Recent advances in our knowledge of the pathogenesis of AD have posited the relationship between skin barrier abnormalities and immune dysregulation [23]. The genetic predisposition of an individual to make IgE antibody responses to common environmental or food allergens has been shown to be strongly associated with AD [24]. Elevated serum IgE is also commonly found in children with INS [9, 12–17]. Two possible explanations of our findings is that AD has a positive influence on the development of INS or that these conditions may share common early life determinants.

INS is defined by the association of the clinical features of NS with renal biopsy findings of diffuse foot process effacement as revealed by electron microscopy. MCD is the most common form of INS in children [27]. To date, the role of the immune system in the pathogenesis of INS remains unclear. MCD is considered to be a T-cell-mediated disease. Circulating factors are released from activated T-cells, which may alter podocyte function, resulting in increased glomerular permeability and massive proteinuria [27]. Recently, several investigators have also found elevated IgE levels in the serum of NS patients. Allergy is well-known as a T-helper 2 (Th2)-driven and IgE-mediated chronic inflammation of a target organ.

Activated Th2 cells express interleukins (IL) 4, 5, and 13 [28, 29]. IL-4 and IL-13 are important in B-cell IgE isotype switching [28, 29], and IL-13 is also involved in the modulation of eosinophilic inflammation and the recruitment of monocytes and T-cells [28, 29]. Serum levels of IL-5 and IL-13 are higher in patients with steroid-sensitive NS before compared with after treatment [30]. CD3+ IL-13-producing cells are increased in children with NS in relapse [31]. Lai et al. reported that IL-13 overexpression in rats led to podocyte injury with downregulation of nephrin, podocin and dystroglycan and upregulation of B7-1 (also termed CD80) in glomeruli [32]. Induction of B7-1 in podocytes has been found to disrupt the filtration barrier, resulting in proteinuria [33, 34]. These findings support our results with regard to the relationship between AD and INS. More recently, MCD has been proposed to be a podocyte disorder mediated by a “2-hit” mechanism. First, CD 80 is induced in podocytes by circulating cytokines (such as IL-13), microbial products, or allergens; second, due to T-regulatory-cell dysfunction and/or impaired CD80 autoregulation, sustained podocyte injury results in MCD [33–36]. Our findings are consistent with this “2-hit” theory.

The strength of our study is that it is the first population-based cohort study to investigate the precise quantification of the incidence of INS in children with AD. Our results revealed an increased incidence rate and risk of INS in the cohort of children with AD. Risk further increased with the severity of AD symptoms. The relationship was consistent regardless of age, gender, or socioeconomic status; these associations were not analyzed in previous studies. Second, our study is a population-based study that minimizes the selection bias inherent in case–control studies. Third, the diagnosis of AD by a physician rather than by questionnaire minimizes both selection and recall bias. Fourth, we adjusted for possible

confounding factors, including age, gender, urbanization of residence area, and parental occupation.

There are a number of limitations to this study. Clinical details, such as medication response and laboratory data, were lacking in the database. A number of possible confounding variables, including genetic and behavioral factors, were also not assessed. Lastly, the subject population of this study is Chinese, and our results may not be representative of other populations.

In conclusion, this population-based cohort study revealed a significantly increased incidence rate of INS in children with AD. In the future, additional research should be conducted to explore the contribution of allergic disease to the development of NS and provide potential strategies of diagnosis and treatment.

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