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Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors

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Summary

Background Hereditary and environmental factors contribute to the occurrence of atopic dermatitis (AD). However, the interaction of these two factors is not totally understood.

Objectives To evaluate the early risk factors for infantile AD at the age of 6 months and to develop a predictive model for the development of AD.

Methods In 2005, a representative sample of mother and newborn pairs was obtained by multistage, stratified systematic sampling from the Taiwan national birth register. Information on hereditary and environmental risk factors was collected by home interview when babies were 6 months old. Multivariate regression analysis was applied to determine the risk factors for AD in the infants.

Results A total of 20 687 pairs completed the study satisfactorily. AD was diagnosed in 7·0% of 6-month-old infants by physicians. Parental asthma, atopic dermatitis and allergic rhinitis, and maternal education levels were risk factors for AD in infants. Among environmental factors, fungus on walls at home and renovation/painting in the house during pregnancy were significantly associated with early infantile AD. Using these factors, the probability of having infantile AD was estimated and grouped into low, high and very high. With five runs of tests in mutually exclusive subsets of this population, the likelihood of AD for 6-month-old infants was consistent in all the groups with the predictive model. The highest predicted probability of AD was 70·1%, among boys with maternal education levels > 12 years, both parents with AD, renovation and painting of the house during pregnancy and fungus on walls at home. The lowest probability was 3·1%, among girls with none of the above factors.

Conclusions This investigation provides a technique for predicting the risk of infantile AD based on hereditary and environmental factors, which could be used for developing a preventive strategy against AD, especially among those children with a family history of atopy.

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Atopic dermatitis (AD) is the most common skin disorder in children and is often the first step in the atopic progression.[1–3] About 50% of children with AD develop asthma and allergies.[3,4] Approximately 50% of children with AD develop symptoms within the first 6 months of life and nearly 85% of individuals with eczema have onset of symptoms by the age of 5 years.[5] The quality of life of children with AD and their families is obviously affected, especially in those children with moderate and severe symptoms.[6–8]

The prevalence of AD has increased in the past two decades worldwide, including Taiwan.[9–13] In previous surveys of schoolchildren in Taiwan, the prevalence of AD was 1·57% in 1995–96 and 2·79% in 2001.[14] Although genetic and environmental factors may interact in the development of AD,[15–17] environmental factors probably play a more important role than genetic effects in the change in prevalence of AD over a short period.

Most of the previous epidemiological studies on AD have focused on preschool or school children.[18] However, as symptoms of AD start early in human life, important life and environmental factors cannot be studied in detail if the participants are preschool children or older. A birth cohort study therefore

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is of value for investigating the prenatal and early postnatal risk factors for AD.

The Taiwan Birth Cohort Study (TBCS) was the first national birth cohort study in Taiwan. The objectives of the TBCS included understanding the growth curve of children in Taiwan, investigating the effects of social and environmental factors on children's growth and health, and exploring growth and health conditions of the children born to foreign mothers.

The purpose of this study was to investigate the effects of hereditary and early environmental factors on AD in 6-month-old infants enrolled in the TBCS. Using these risk factors, a model was set up for predicting the risk of AD in infants.

Materials and methods

Subject recruitment and sampling

A nationwide birth register was started in 2000 by the Department of Health. All medical institutions responsible for delivering babies are required to report information to the Department of Health including the demographics and vital status of the newborn children. The TBCS pilot study[19] was conducted from July 2003, including a smaller sample of mother–fetus pairs. For the main TBCS study, representative samples were obtained by a multistage stratified systematic sampling design according to the Taiwan national birth registration data. Based on the administrative division (four strata: county, town, city and area) and the total fertility rate (three strata: low, medium and high), 369 townships in Taiwan were split into 12 strata. A total of 88 townships were randomly selected from the 12 strata by using the principle of proportion probability to size. Beginning in January 2005, newborn candidates and their mothers were randomly sampled from study areas every month. A total of 24 200 pairs of mothers and their newborn infants were recruited into the TBCS. These infants were followed up by home interview at the age of 6 months, 18 months and 3 years. A home interview was implemented after the mother's informed consent by 89 well-trained interviewers who had at least 2 years' experience of questionnaire interviews conducted by the Bureau of Health Promotion, Taiwan.

Data collection

Structured questionnaires were used to collect demographic data, history of atopic diseases (asthma, allergic rhinitis and AD) in the parents, indoor environmental conditions and the health status of the babies.

The following question to the main carer was used to determine the presence of AD in the infants at 6 months of age, 'Has this baby ever had physician-diagnosed atopic dermatitis?' Information about birth order and characteristics, vaccination and breastfeeding were collected by questionnaire. Enquiries were made about environmental factors including incense burning at home, carpet use, pet raising, fungus on walls, painting and renovation at home during pregnancy and presence of cockroaches in the home.

Statistical analyses

Statistic analyses were performed with statistical software JMP version 5.0.1 (SAS Institute Inc., Cary, NC, U.S.A.). Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess statistical associations between potential risk factors and infantile AD. Because multiple comparisons were done for univariate effects on AD, the P-value was adjusted. Therefore, $P \leq 0{\cdot}01$ was considered to be statistically significant.

As boys and girls have different lifetime prevalences of AD, participants were stratified by sex for the determination of risk factors and for setting up the predictive models. Backward stepwise regression was applied to select significant factors in the predictive model. A mutually exclusive group of 20% of all participants was randomly selected for testing the predictive model. For boys and girls, respectively, five runs of the predictive modelling were carried out. The prediction probability of AD was calculated by the equation, probability = $1 - (1/[1 + E\ \{\text{logical training model}\}])$.[20] For each run, the risks were categorized into < 8%, 8–16% and > 16% for boys, and < 6%, 6–12% and > 12% for girls. The true percentage of boys and girls in each category was calculated.

Results

Among the 24 200 sampled participants, 2952 of the mother–infant pairs were lost because of incorrect addresses (n = 358), refusal to be interviewed (n = 1734), moved abroad (n = 351), no one at home after multiple visits (n = 104), death of the infant (n = 67) and other reasons (n = 338). A total of 21 248 participants (87·8%) completed the first interview when the babies were 6 months old during July 2005 to July 2006. We further excluded multiparity (n = 561), resulting in a total of 20 687 babies who were included in the final analysis. The prevalence of AD was 7·0% in the babies at the age of 6 months. The demographic data of parents and babies are shown in Table 1. Approximately half the babies (51·1%) were the first child of the participating mothers. One-third of the babies were born by caesarean section. The prevalence of low birth weight (< 2500 g in birth weight) and premature birth (< 37 weeks of gestation) was 7·0% and 5·4%, respectively (data not shown). The mean duration of breastfeeding was 1·9 months. The mean age of the mothers was 29·3 years and of the fathers, 33·3 years. AD was more prevalent in boys (8·1%) than in girls (5·7%). Among parental atopic diseases, the most prevalent was allergic rhinitis (Table 2). More than 45% of the parents graduated from college or higher education (Table 2).

Table 2 shows the significant factors for AD in 6-month-old babies. Sex of the baby was significantly associated with infantile AD. Parental education was positively associated with AD. Parents with atopic disease, especially AD, had a strong effect for infantile AD. Among environmental factors, we found that

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Table 1 Demographic data of the 6-month-old babies included in the study and their parents (n = 20 687)

Variables	
Atopic dermatitis, n (%)	
Yes	1438 (7·0)
No	19 249 (93·0)
Gestation length (weeks), mean ± SD	38·5 ± 1·5
Birthweight (g), mean ± SD	3216 ± 428
Breastfeeding duration (months), mean ± SD	1·93 ± 2·14
Birth order, n (%)	
1st child	10 559 (51·1)
2nd child	7902 (38·2)
≥ 3rd child	2214 (10·7)
Delivery method, n (%)	
Natural delivery	13 905 (67·2)
Caesarean section	6769 (32·7)
Mother menarche (years), mean ± SD	13·40 ± 1·43
Maternal age (years), mean ± SD	29·33 ± 4·87
Paternal age (years), mean ± SD	33·28 ± 5·66

Some numbers do not add up to the total number of participants because of missing data.

fungus on walls, house renovation during pregnancy and painting of the house were significantly associated with AD. However, carpets in the house, having pet(s) in the house and incense burning had no significant effect for AD (data not shown).

Due to the high correlation between renovation and painting of the house during pregnancy ($P < 0·0001$), we combined these two factors in a multiple regression analysis. After adjusting for covariates in regression analysis, we found that the most important heredity effect factors for infantile AD were parents with AD and allergic rhinitis. Among environmental factors, fungus on walls in the home and renovation/painting at home during pregnancy were the most important (Table 2). We therefore included these factors in the predictive models. The proposed β values of heredity and environmental and confounding factors are given in Table 3.

Table 4 shows the risk categorization based on the estimated probability of AD, and the true proportion of physician-diagnosed AD in each category in five mutually exclusive subpopulations of infant boys and girls. The data demonstrated that the true proportion of boys and girls having AD was consistent with our prediction in both boys and girls.

Figure 1 demonstrates the predictive probability of risk for AD by different characteristics of heredity, environmental factors and maternal education in boys and girls. According to the variables shown in Table 3, there would be 108 values for predicted probabilities of AD development in 6-month-old boys and 108 values for those in girls. Due to limited space, only 16 predictive values are listed for each gender. Among boys, the highest predicted probability of AD was 70·1% when maternal education levels were more than 12 years, both parents had AD, with renovation and painting of the house during pregnancy and visible fungus on walls at home. The lowest probability in boys was 4·2% when none of the above factors were present (Fig. 1a). For girls, the highest and lowest predicted probabilities were 55·0% and 3·1%, respectively (Fig. 1b).

Discussion

The TBCS was the first national representative birth cohort study in Taiwan. Using this cohort approach, we established a predictive model for the probability of infantile AD at the age of 6 months. Our results show that parental education levels, parents with atopic diseases and environmental factors such as fungus on walls at home and renovation/painting of the house during pregnancy are important factors for predicting the risk of AD in 6-month-old infants.

Parental atopy is an important risk factor for atopic disease in children. In our previous study among schoolchildren, parental atopy was strongly associated with AD in children.[18] A study involving three Chinese populations also reported a very strong effect of family history of allergic diseases on eczema.[21] A maternal history of AD seems to have stronger effects than a paternal history of AD.[22,23] However, in our investigation, maternal and paternal atopy, when asthma, allergic rhinitis and AD were considered together, appeared to contribute similarly to infant AD.

Renovation and painting in the house during pregnancy were found to be significant factors for AD in this study. Poor air quality has been reported to be associated with the risk for irritative and allergic symptoms among adults and children.[24,25] Increasing concentrations of microorganisms, including fungi were measured in a hospital during renovation.[26] Indoor renovation with wall painting, new floor coverings and new furniture was also related to an increased risk of allergic symptoms and eczema. Such effects were more prominent when redecoration was done during pregnancy.[27] New surface materials, new furniture and paint contain and release many chemical compounds, such as biocides, surfactants, pigments, binders, amines, monomers and solvents. Many of these are reported to be associated with allergic diseases.[28] Allergen-specific responses seen in AD are found skewed towards T-helper (Th) 2 phenotypes, including high levels of interleukin (IL)-4 and elevated levels of IgE in serum.[29,30] Volatile organic compounds (VOCs) were reported to transfer through the placenta to the fetus and to affect neonatal immune status by elevating IL-4 production and reducing interferon-γ production.[31] Moreover, VOCs were found to damage the skin barrier function and enhance the adverse effects of house dust mites on sensitized patients with AD.[32] Our study shows that renovation and painting during pregnancy could contribute to infantile AD. However, the exact causal agents and the exposure mechanisms warrant further investigation.

We also found that fungus on the walls of the home was significantly associated with AD. Taiwan has tropical and

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Table 2 Factors and unadjusted and mutually adjusted odds ratios (OR, AOR) for atopic dermatitis (AD) in the 6-month-old babies (n = 20 687)

Variables	No. of subjects	No. with AD (%)	OR (95% CI)	AOR (95% CI)
Sex				
Boy	10 845	873 (8·05)	1·44 (1·29–1·60)***	1·44 (1·28–1·61)***
Girl	9842	565 (5·74)	Reference	Reference
Maternal education				
High	9305	856 (9·20)	3·44 (2·77–4·33)***	1·78 (1·36–2·35)***
Middle	8271	493 (5·96)	2·15 (1·72–2·73)***	1·52 (1·19–1·98)**
Low	3075	88 (2·86)	Reference	Reference
Paternal education				
High	9434	870 (9·22)	2·35 (1·94–2·87)***	1·33 (1·05–1·69)*
Middle	8212	443 (5·39)	1·32 (1·08–1·63)**	1·01 (0·81–1·27)
Low	2871	119 (4·14)	Reference	Reference
Maternal asthma				
Yes	312	41 (13·14)	2·06 (1·45–2·84)***	1·71 (1·18–2·41)**
No	20 375	1397 (6·86)	Reference	Reference
Paternal asthma				
Yes	245	27 (11·02)	1·67 (1·09–2·45)***	1·35 (0·87–2·02)
No	20 442	1411 (6·90)	Reference	Reference
Maternal AD				
Yes	669	143 (21·38)	3·93 (3·23–4·76)***	2·85 (2·32–3·49)***
No	20 018	1295 (6·47)	Reference	Reference
Paternal AD				
Yes	606	130 (21·45)	3·92 (3·19–4·78)***	2·94 (2·36–3·63)***
No	20 081	1308 (6·51)	Reference	Reference
Maternal AR				
Yes	3150	325 (10·32)	1·70 (1·49–1·93)***	1·32 (1·15–1·52)***
No	17 537	1113 (6·35)	Reference	Reference
Paternal AR				
Yes	3321	363 (10·93)	1·86 (1·64–2·11)***	1·50 (1·32–1·72)***
No	17 366	1075 (6·19)	Reference	Reference
Fungus on walls				
High (> 1)	3179	264 (8·40)	1·29 (1·13–1·47)***	1·23 (1·07–1·42)**
Low (1)	4227	336 (7·95)	1·37 (1·18–1·58)***	1·33 (1·13–1·57)***
No	13 274	835 (6·29)	Reference	Reference
House renovation during pregnancy				
Yes	808	85 (10·52)	1·61 (1·27–2·02)***	–[a]
No	19 857	1352 (6·81)	Reference	
House painting during pregnancy				
Yes	535	60 (11·21)	1·72 (1·30–2·24)***	–[a]
No	20 128	1177 (6·84)	Reference	
Painting furniture/renovation in the house during pregnancy				
Painting and renovation	300	38 (12·67)	1·99 (1·39–2·78)***	1·67 (1·15–2·36)**
Painting or renovation	743	69 (9·29)	1·41 (1·08–1·80)**	1·29 (0·99–1·67)
No	19 619	1330 (6·78)	Reference	Reference

CI, confidence interval; AR, allergic rhinitis. AOR was adjusted by birth order, birth weight, breastfeeding, maternal age at delivery, maternal weight gain in pregnancy, maternal ethnicity, maternal menarche, postpartum depression, cockroaches, water damage and factors as shown in the Table. *P < 0·05, **P < 0·01, ***P < 0·001. [a]None in the multiple regression analysis. Some numbers do not add up to the total number of participants because of missing values.

subtropical regions; a high year-round average temperature of 15–30 °C and a relative humidity of 70–80% provide an environment suitable for fungi and dust mites to grow. Fungi are well-known indoor allergens for asthma and allergic rhinitis and indoor exposure to certain airborne fungi such as *Aspergillus* and *Penicillium* was shown to be a risk factor for asthma, atopy and respiratory symptoms in children.[33] A previous study on schoolchildren in Taiwan also demonstrated a higher risk of developing eczema associated with more walls with visible mould at home.[18] *Malassezia furfur*, a species of Basidiomycota, was reported to be related to AD development[34] as more than 40% of patients with AD had a positive radioallergosorbent test (RAST), atopy patch test or skin test for *M. furfur*. *Candida albicans* was reported to induce a Th2-type response and to play a role in atopic eczema dermatitis syndrome.[35] High levels of specific IgE against *Alternaria* and *M. furfur* were also measured in patients with AD.[36,37] However, such immunological markers for moulds could simply be epiphenomena associated

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Table 3 The proposed β values for the predictive model for atopic dermatitis (AD) in boys and girls

Factors[a]	Boys	Girls
Constant	−3·13	−3·43
Hereditary factors		
Maternal		
AD (+)	1·19	1·20
AD (−) and AR (+)	0·36	0·29
None	0	0
Paternal		
AD (+)	1·37	1·13
AD (−) and AR (+)	0·43	0·55
None	0	0
Environmental factors		
Fungus on walls		
Yes	0·25	0·23
No	0	0
Painting furniture/renovation in the house during pregnancy		
Painting and renovation	0·60	0·60
Painting or renovation	0·27	0·30
No	0	0
Maternal education		
> 12 years	0·57	0·47
≤ 12 years	0	0

AR, allergic rhinitis. [a]All factors were put in multiple regression model.

with simultaneous allergic rhinitis or asthma. Patients with AD have skin barrier dysfunction and increased transepidermal water loss. This impairment of the skin barrier function causes increased allergen absorption which contributes to the cutaneous hyper-reactivity of AD.[38] Whether or not reported fungus on the walls is associated with increased fungal contact and penetrating dysfunctional skin will be an important subject for future study.

There are limitations to this study. Firstly, infantile AD was based on mother-reported physician-diagnosed AD. We did not inquire if this diagnosis was made by a paediatrician, a dermatologist or a general practice physician. However, this diagnosis is most likely to be made by a member of one of these specialties. Whether the eczema was the primary reason for consultation or if it was diagnosed in a routine visit was not questioned either. Therefore misclassification into AD could have occurred. However, such misclassification was probably not different in different exposure groups, and therefore unlikely to bias the study results. Secondly, 2952 babies were lost from the recruitment in our study, among them, 1734 because of refusal to participate. Selection bias might have been a concern. However, as the interviewers and the interviewees were unaware of the main hypothesis, the predictor and the outcome variables, selection bios caused by differential participation was less likely. Finally, the exposure levels of environmental factors were based on the questionnaire, and not a true exposure assessment. This introduced misclassification in environmental exposure. Further investiga-

Table 4 Categories of atopic dermatitis (AD) risk by each test run of the predictive model, and the true proportion (%) of AD in each category in boys and girls[a]

Category of AD risk	Boys						Girls					
	eP (%)	Run 1	Run 2	Run 3	Run 4	Run 5	eP (%)	Run 1	Run 2	Run 3	Run 4	Run 5
Low	< 8	81/1477 (5·5)	79/1423 (5·6)	76/1511 (5·0)	88/1432 (6·2)	77/1458 (5·3)	< 6	45/1325 (3·4)	61/1302 (4·7)	47/1287 (3·7)	42/1252 (3·4)	48/1304 (3·7)
High	8–16	56/567 (9·9)	67/619 (10·8)	53/529 (10·0)	63/604 (10·4)	74/573 (12·9)	6–12	39/534 (7·3)	44/544 (8·1)	59/566 (10·4)	65/168 (10·5)	43/581 (7·4)
Very high	≥ 16	36/120 (30·0)	27/121 (22·3)	35/123 (28·5)	27/127 (21·3)	33/133 (24·8)	≥ 12	11/103 (10·7)	12/115 (10·4)	20/107 (18·7)	14/89 (15·7)	14/80 (17·5)

eP, expected probability. [a]Probability (P) was calculated by the equation, $P = 1 - 1/\{1 + E[\text{training logical model}]\}$.[20]

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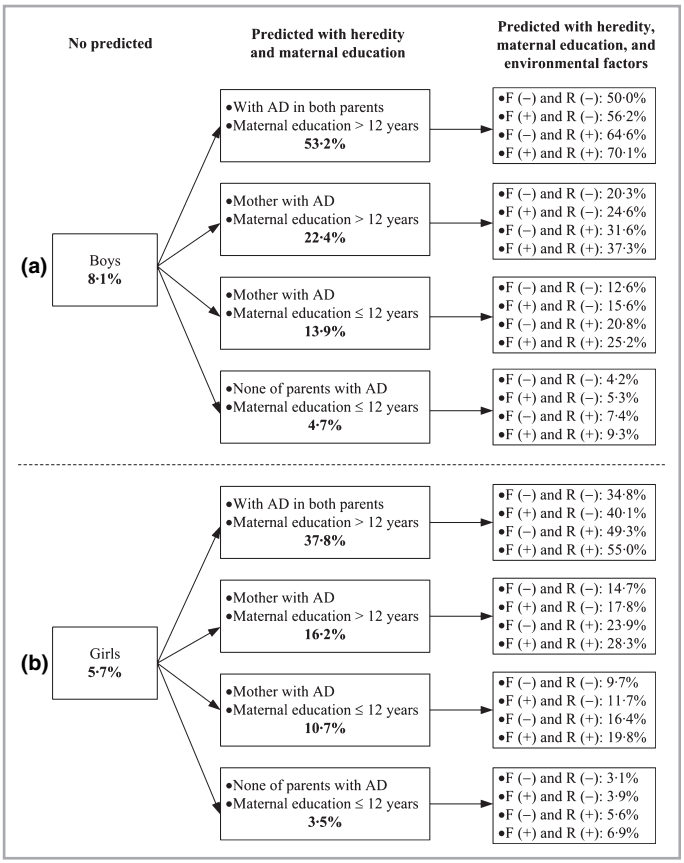

Fig 1. The predictive probability of atopic dermatitis (AD) in 6-month-old infants by hereditary and environmental factors, and maternal education. The left column shows the probability of AD without predictive variables. The central column demonstrates the probability of AD predicted with hereditary factors and maternal education. The right column shows the predicted probability of AD when taking into consideration the environmental factors, i.e. fungus on walls, and renovation and painting of the house during pregnancy. (a) The predictive results of boys. (b) The predictive results of girls. F (+), with fungus on walls at home; F (−), without fungus on walls at home; R (+), with renovation and painting of the house; R (−), without renovation and painting of the house.

tion to quantify the environmental exposure will be needed to provide more accurate health effects of such factors.

The strengths of the study include the generally population-based cohort design and large sample size. The two-stage sampling including urban, suburban and rural populations and considering the fertility of different administrative regions can enhance the representativeness of newborns in Taiwan. Furthermore, the birth cohort study design allows for investigation on early predictors for child health.

In conclusion, we established a predictive model for infantile AD in boys and girls based on hereditary and environmental factors. This approach allows for identification of high-risk infants, and for the application of environmental preventive measures.

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