Maternal and paternal atopic dermatitis and risk of atopic dermatitis during early infancy in girls and boys

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Clinical Implications

- Parental atopic dermatitis increases the risk of atopic dermatitis in infancy, particularly in offspring of the same sex as the affected parent. This may be an important factor to consider when selecting infants for primary prevention strategies.

TO THE EDITOR:

Parental allergic diseases, particularly atopic dermatitis (AD), have been established as major risk factors for AD in offspring,[1] with some studies reporting a greater risk from maternal AD than from paternal AD.[2] In the Isle of White study with a cohort of more than 1400 children aged 1 to 18 years, Arshad et al[3] found an increased risk of AD in female, but not male, offspring of mothers with AD, and in male, but not female, offspring of fathers with AD.[3]

Genetic factors may play a more important role in the pathogenesis of AD presenting early, rather than later, in life.[4] Following up on the findings of Arshad et al, we aimed to determine whether AD in fathers and mothers increases the risk of AD during early infancy in their sons and daughters. From the general population-based mother-child birth cohort in Norway and Sweden, Preventing Atopic Dermatitis and Allergies in Children (PreventADALL) study,[5] we included all 1155 infants not randomized to early skin care intervention, who had clinical assessment at age 3 and/or 6 months and available information on parental atopic disease (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Recruitment of pregnant women occurred from December 2014 through October 2016. The infants, 617 boys and 538 girls, were born at gestational week 35 or later. Information on parental doctor-diagnosed AD was collected by electronic questionnaires sent to the mother at weeks 18 and 34 of pregnancy. Skin assessment of the infants was performed by trained health care personnel, and additional skin symptoms and signs were recorded in electronic questionnaires by parents at 3 and 6 months.

The primary outcome, used as a proxy for AD, was *possible AD* (pAD), defined as observed eczema in infants by study personnel, excluding differential diagnoses to AD, and/or parent-reported intermittent or persistent itchy exanthema in their child for more than 4 weeks. Odds ratios (ORs) from sex-stratified analysis were used to assess the association of maternal and paternal AD with pAD at age 3 and 6 months. A logistic regression model was used to test for interaction between sex of the child and parental AD. Because AD is a strong risk factor for other allergic diseases, we did not adjust for parental AD comorbidities. The possibility of confounding variables was considered to be low.

At age 3 and 6 months, regardless of sex, only paternal AD significantly increased the risk of pAD in the offspring, with ORs of 1.80 and 1.81, respectively (Table I). When stratified by offspring sex, the parental effects were statistically significant at 6 months only, with an increased risk from mothers to daughters (OR, 1.79; 95% CI, 1.07-3.00) and from fathers to sons (OR, 2.36; 95% CI, 1.34-4.20) (Table II). When defining the offspring phenotype as pAD at age 3 *and/or* 6 months, the same sex-specific pattern was seen (Table II). No significant effects were found on pAD from parental AD to the group of offspring of opposite sex. When using the full regression model, a non-statistically significant interaction was found for maternal AD and offspring sex by age 6 months ($P = 0.09$) while the other interactions shown in Table E2 in this article's Online Repository at www.jaci-inpractice.org had a P value of more than .1. Significant associations with offspring sex were seen in all logistic regression models, adding further support to the theory of a sex-dependent risk increase (see Table E2).

To our knowledge, this is the first study observing a sex-specific increased risk of AD in early infancy associated with parental AD. We found an increased risk of AD in female offspring by maternal AD and in all offspring by paternal AD, with some evidence of a stronger paternal effect in boys than in girls. The maternal signal in girls and paternal signals in boys were stronger and significant at age 6 months, yet present but not significant at age 3 months. The sex-related AD risk is in line with results of Arshad et al,[3] showing a sex-dependent risk increase for AD in childhood and adolescence. The lack of statistically significant interactions between parental AD and offspring sex is partially in line with their findings, but in contrast to the significant interaction of maternal AD and AD in females from age 1 to 18 years. Our study is less powered to detect interaction effects than their study with its repeated measures in more than 1400 subjects over a 17-year time period.[3]

Possible differential effects on AD by maternal and paternal AD could be explained by genomic imprinting, that is, an epigenetic phenomenon that causes a specific parental allele to be expressed in a parent-of-origin specific manner, silencing the corresponding allele through DNA-methylation or histone modifications[6,7]; thus, the localization of a susceptibility gene for AD to an imprinted region could influence the inheritance pattern. Recent publications have also suggested that the Y chromosome influences the immune system and inflammatory responses in males.[8]

A strength of our study is the high number of infants recruited from the general population in 3 geographically different areas in Norway and Sweden and with data from both questionnaires and

TABLE I. pAD and OR for pAD in infants with or without parental AD

Age	Maternal AD pAD, % (n/N)	No maternal AD pAD, % (n/N)	OR (95% CI)	Paternal AD pAD, % (n/N)	No paternal AD pAD, % (n/N)	OR (95% CI)
3 mo	15 (33/221)	12 (92/788)	1.33 (0.87-2.04)	19 (22/118)	11 (98/869)	**1.80 (1.08-3.00)**
6 mo	27 (57/214)	22 (169/759)	1.27 (0.90-1.80)	33 (38/116)	21 (177/834)	**1.81 (1.19-2.76)**
3 and/or 6 mo	31 (70/224)	27 (214/794)	1.23 (0.89-1.70)	39 (46/119)	26 (225/876)	**1.82 (1.22-2.72)**

Statistically significant ORs are given in bold.

TABLE II. pAD and OR for pAD in (A) girls and (B) boys with or without parental AD

A. Girls

Age	Maternal AD pAD, % (n/N)	No maternal AD pAD, % (n/N)	OR (95% CI)	Paternal AD pAD, % (n/N)	No paternal AD pAD, % (n/N)	OR (95% CI)
3 mo	13 (13/103)	10 (35/362)	1.35 (0.69-2.66)	16 (9/58)	9 (37/402)	1.81 (0.83-3.98)
6 mo	28 (28/102)	17 (61/350)	**1.79 (1.07-3.00)**	24 (14/58)	19 (74/387)	1.35 (0.70-2.59)
3 and/or 6 mo	32 (34/105)	22 (79/365)	**1.73 (1.07-2.80)**	33 (19/58)	23 (92/405)	1.66 (0.91-3.00)

B. Boys

Age	Maternal AD pAD, % (n/N)	No maternal AD pAD, % (n/N)	OR (95% CI)	Paternal AD pAD, % (n/N)	No paternal AD pAD, % (n/N)	OR (95% CI)
3 mo	17 (20/118)	13 (57/426)	1.32 (0.76-2.30)	22 (13/60)	13 (61/467)	1.84 (0.94-3.60)
6 mo	26 (29/112)	27 (108/409)	0.97 (0.61-1.57)	41 (24/58)	23 (103/447)	**2.36 (1.34-4.20)**
3 and/or 6 mo	30 (36/119)	32 (135/429)	0.95 (0.61-1.47)	44 (27/61)	23 (133/471)	**2.02 (1.17-3.48)**

Statistically significant ORs are given in bold.

clinical investigations. The risk of biased reporting of parental AD after subsequent development of eczema in offspring was avoided because of the prospective study design. To limit the risk of misclassification of AD in early infancy, we used prespecified UK Working Party criteria modified for early infancy, as described in the "Outcome Definitions" section in this article's Online Repository at www.jaci-inpractice.org. Mothers completing the questionnaires may have reported AD, particularly in fathers with a persistent phenotype not limited to childhood. This, however, cannot account for the differential effects seen from maternal and paternal AD in girls and boys.

Our findings indicate a higher risk from maternal and paternal AD for AD in early infancy in offspring of the same sex as the affected parent. Although the associations were statistically significant at age 6 months only, our findings may provide a rationale for sex-specific risk stratification for primary prevention interventions.

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ONLINE REPOSITORY

OUTCOME DEFINITIONS

In the PreventADALL study, we have defined the following 3 levels of AD:

Level 1. AD: UK Working Party criteria and/or Hanifin and Rajka criteria are met.

Level 2. Eczema: Observed eczema at clinical investigations, clinically excluding common differential diagnosis to AD.

Level 3. pAD: All cases where AD has been suspected at the clinical investigations (observed eczema) and/or from parents reporting presence of an itchy rash for at least 4 weeks (from the UK Working Party criteria).

TABLE E1. Characteristics for the 1155 infants with available information on the exposure (ie, parental history of AD) and outcome (ie, pAD at 3- and/or 6-mo follow-up)

Characteristic	No AD (N = 833)	pAD (N = 322)	*P* value	Total (N = 1155)
Age mother (y), mean ± SD (min-max) (N = 1155)	32.6 ± 4.1 (21.0-48.0)	32.6 ± 4.0 (22.0-43.0)	.92	32.6 ± 4.1 (21.0-48.0)
Age father (y), mean ± SD (min-max) (N = 1005)	34.7 ± 5.5 (21.0-72.0)	35.0 ± 5.5 (23.0-65.0)	.48	34.8 ± 5.5 (21.0-72.0)
Mother Nordic origin, n (%) (N = 1072)	711 (91.5)	266 (90.2)	.49	977 (91.1)
Father Nordic origin, n (%) (N = 1050)	687 (90.2)	252 (87.5)	.21	939 (89.4)
Education mother, 4 y of university or more, n (%) (N = 1066)	444 (57.5)	181 (61.6)	.23	625 (58.6)
Education coparent, 4 y of university or more, n (%) (N = 1027)	371 (49.7)	136 (48.6)	.76	507 (49.4)
Family income, n (%) (N = 1056)*				
Low	114 (14.9)	41 (14.0)	.72	155 (14.7)
Middle	563 (73.7)	207 (70.9)	.36	770 (72.9)
High	87 (11.4)	44 (15.1)	.11	131 (12.4)
BMI, mother at 18 wk of pregnancy, mean ± SD (min-max) (N = 1137)	24.8 ± 3.6 (18.3-39.7)	24.8 ± 3.6 (17.2-41.4)	.73	24.8 ± 3.6 (17.2-41.4)
≥1 previous parity, n (%) (N = 1072)	317 (40.8)	126 (42.7)	.57	443 (41.3)
Allergic disease mother, n (%) (N = 1072)	488 (62.8)	204 (69.2)	.11	692 (64.6)
Allergic disease father, n (%) (N = 1072)	367 (47.4)	172 (57.7)	.01	539 (50.3)
AD mother, doctor diagnosed, n (%) (N = 1018)	154 (21.0)	70 (24.6)	.21	224 (22.0)
AD father, doctor diagnosed, n (%) (N = 995)	73 (10.1)	46 (17.0)	.003	119 (12.0)
Asthma mother, doctor diagnosed, n (%) (N = 1050)	134 (17.7)	58 (19.9)	.39	192 (18.3)
Asthma father, doctor diagnosed, n (%) (N = 1041)	107 (14.3)	44 (15.1)	.75	151 (14.5)
Allergic rhinitis mother, doctor diagnosed, n (%) (N = 905)	167 (25.3)	62 (25.4)	.96	229 (25.3)
Allergic rhinitis father, doctor diagnosed, n (%) (N = 952)	166 (23.9)	82 (32.0)	.01	248 (26.1)
Food allergy mother, doctor diagnosed, n (%) (N = 947)	103 (14.7)	41 (16.6)	.48	144 (125.2)
Food allergy father, doctor diagnosed, n (%) (N = 981)	67 (9.3)	31 (11.9)	.24	98 (10.0)
Lifestyle during pregnancy, n (%)				
Smoking (N = 1155)	40 (4.8)	10 (3.1)	.20	50 (4.3)
Live rural (N = 1072)	71 (9.1)	21 (7.1)	.29	92 (8.6)
Pets in general (N = 1072)	195 (25.1)	60 (20.3)	.10	255 (23.8)
Cat (N = 924)	84 (12.6)	23 (8.9)	.12	107 (11.6)
Dog (N = 965)	113 (16.3)	35 (13.0)	.20	148 (15.3)
Cat and dog (N = 834)	13 (2.2)	4 (1.7)	.64	17 (2.0)
Cesarean section, n (%) (N = 1148)				
Elective (N = 1035)	41 (5.5)	24 (8.4)	.09	65 (6.3)
Acute (N = 1129)	80 (10.2)	33 (11.1)	.64	113 (10.4)
Gestational age at birth (wk), mean ± SD (min-max) (N = 1138)	39.2 ± 1.7 (35.0-42.9)	39.4 ± 1.6 (35.2-45.9)	.08	39.3 ± 1.7 (35.0-42.9)
Sex: female, n (%) (N = 1155)	405 (48.6)	133 (41.3)	.03	538 (46.6)
Birth weight (kg), mean ± SD (minimum-maximum) (N = 1132)	3.5 ± 0.5 (1.9-4.9)	3.6 ± 0.5 (2.2-5.1)	.02	3.6 ± 0.5 (1.9-5.1)
Born during winter season (October-March), n (%) (N = 1155)	460 (55.2)	180 (55.9)	.84	640 (55.4)

BMI, Body mass index.

*Income before taxes in Norwegian kroner (NOK): Low = <600,000 NOK; Middle = 600,000-1,400,000 NOK; High = >1,400,000 NOK.

TABLE E2. Logistic regression models examining the interaction effect of parental history of AD with offspring sex at age 3, 6, and 3 and/or 6 mo by the conceptual model: pAD ~ paternal AD (yes/no) + maternal AD (yes/no) + sex (male/female) + maternal AD × sex + paternal AD × sex*

Variables in the equation	pAD at 3 mo			pAD at 6 mo			pAD at 3 and/or 6 mo		
	P value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI
Paternal AD	.14	1.72	0.83-3.53	.02	2.09	1.15-3.82	.04	1.86	1.04-3.33
Maternal AD	.99	1.00	0.53-1.88	.99	1.00	0.59-1.67	.69	0.90	0.56-1.47
Sex	.02	0.52	0.30-0.90	.03	0.64	0.42-0.96	.002	0.56	0.38-0.81
Paternal AD × sex	.70	1.24	0.41-3.78	.62	0.79	0.32-1.98	.79	1.13	0.48-2.66
Maternal AD × sex	.40	1.53	0.57-4.08	.18	1.68	0.79-3.61	.09	1.87	0.91-3.82

*Parental AD = no and sex = male were set to 0 in the indicator variables.