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

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Parental AD and AD in early infancy

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**Clinical Implications:**

**Parental atopic dermatitis (AD) increases the risk of AD 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.**

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*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 > 1400 children aged 1-18 years, Arshad *et al* 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 if 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 3 and/or 6 months of age and available information on parental atopic disease (Table E1, online repository). Recruitment of pregnant women occurred from December 2014 through October 2016. The infants, 617 boys and 538 girls, were born at gestational week 35.0 or later. Information on parental doctor-diagnosed AD was collected by electronic questionnaires sent to the mother at week 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 pADat 3 and 6 months of age. A logistic regression model was used to test for interaction between sex of the child and parental AD. As AD is a strong risk factor for other allergic diseases, we did not adjust for parental AD co-morbidities. The possibility of confounding variables was considered to be low.

At 3 and 6 months of age, 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 1). 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; 1.07-3.00) and from fathers to sons (OR 2.36; 1.34-4.20) (Table 2). When defining the offspring phenotype as pADat 3 *and/or* 6 months of age, the same sex-specific pattern was seen (Table 2). 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 6 months of age (p =0.09) while the other interactions shown in table E2 had a p-value of >0.1. Significant associations with offspring sex were seen in all logistic regression models adding further support to the theory of a sex-dependent risk increase (Table E2, online repository).

To the best of 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 girls. The maternal signal in girls and paternal signal in boys were stronger and significant at 6 months of age, yet present but not significant at 3 months of age. The sex-related AD risk is in line with those of Arshad *et al*, showing a sex-dependent risk increase for AD in childhood and adolescence (3). 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 1 to 18 years of age. 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, i.e. 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 three geographically different areas in Norway and Sweden and with data from both questionnaires and clinical investigations. The risk of biased reporting of parental AD after subsequent development of eczema in offspring was avoided due to 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 shown in E2. 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 6 months of age only, our findings may provide a rationale for sex specific risk stratification for primary prevention interventions.

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