Differences in Occurrence, Risk Factors and Severity of Early-onset Atopic Dermatitis among Preterm and Term Children

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This prospective birth cohort followed 150 preterm and 300 term newborns during the first year of life to assess possible differences in risk factors, age at onset, anatomical location, and severity of atopic dermatitis. Atopic dermatitis was diagnosed clinically, and severity was assessed using Eczema Area Severity Index (EASI). DNA was analysed for filaggrin gene mutations. Parents were asked about environmental exposures and emollient use. Atopic dermatitis during the first year of life was observed in 21.2% of children and was more common in term children compared with preterm children (26.7% vs 11.7%, p < 0.001), with lower age of onset (4 vs 6 months, p < 0.05) and more severe disease at onset (EASI: 4.8 vs 0.4, p < 0.0005). Environmental risk factors for atopic dermatitis were essentially similar for preterm and term born children, apart from winter and autumn births. Filaggrin gene mutations were less common in preterm than term children (4.1% vs 9.2%, p = 0.06).

Key words: atopic dermatitis; premature birth; risk factors; cohort study.

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Atopic dermatitis (AD) is a chronic, relapsing itchy skin disease (1, 2). Genetically predisposed individuals exposed to exogenous skin stressors along with other environmental exposures, develop dysregulation of the immune system, skin barrier impairment and, in turn, AD (3, 4). Autumn or winter births (5, 6), bathing in hard domestic water (5), or elevated exposure to air pollution (7) have been associated with increased occurrence of AD, whereas neonatal exposure to dogs may decrease the risk (8). Similar, common loss-of-function mutations in filaggrin gene (FLG) are associated with increased risk of AD and early disease onset (9, 10).

Most data on prematurity shows that preterm birth is associated with a reduced risk of developing AD (11–13), but findings are conflicting (14). Altered cutaneous immunology and dysbiosis have been proposed. However, no study has examined whether AD risk factors differ between preterm and term children as well as AD severity, age of AD onset and anatomical localization. This prospective birth cohort study examined risk factors for developing AD during the first year of life in preterm and term children, along with clinical manifestations of AD, including disease severity, anatomical localization and age of AD onset.

SIGNIFICANCE
This prospective birth cohort study showed that preterm birth was associated with a significantly decreased risk of developing atopic dermatitis during the first year of life, as well as a decreased severity of atopic dermatitis at onset. Overall, the study confirmed previous risk factors for atopic dermatitis, but identified slight differences between preterm and term born children.

MATERIALS AND METHODS
Study population
The study birth cohort was approved by the regional ethical committee, Region Hovedstaden (H-16042283 and H-16042294) and conducted according to the Declaration of Helsinki. The BABY Cohort has been described previously in detail, including sample size calculation (15). Briefly, parents of 150 preterm and 300 term newborns were recruited to a prospective study from August 2017 to August 2019 at Rigshospitalet, Copenhagen, and Nordsjællands Hospital, Hillerod, Denmark. Preterm newborns, born below 37+0 of gestational age (GA), without severe congenital abnormalities were enrolled during the first 31 days of life. Term singleton newborns (GA: 37+0 to 41+6) without serious illness and who did not receive antenatal corticosteroids, were enrolled during the first 3 days of life.

Cohort design
Preterm children were scheduled for 2 clinical study visits: as soon as possible after birth, depending on the child’s overall health, and 2 months after the planned due date. Term children were scheduled for 3 clinical study visits: within the first few days of life and at 2 and 12 months. A subgroup of term children was scheduled for 1 clinical study visit at 6 months.
A diagnosis of AD was based on the diagnostic criteria of Hanifin and Rajka, except that we excluded IgE levels and subcapsular cataract.

All parents were instructed to contact the study personnel if the child developed skin lesions that could be eczematous, after which the child participated in an additional clinical visit. At all study visits, detailed information about the child’s skin exposures was obtained. All examinations were performed by medical doctors trained in AD by professors in dermatology.

**Statistics analysis**

Baseline characteristics were presented with frequencies and percentages for categorical variables. Normally distributed continuous variables were presented with mean and standard deviations (SD). Non-normally distributed continuous variables were presented with median and interquartile range (IQR). χ² test and 1-way ANOVA were performed to compare differences between normally distributed variables. Mann–Whitney U test was performed to compare non-normally distributed continuous variables.

Kaplan–Meier curves and hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated using multivariate Cox proportional hazard regression analysis with “development of AD in the first year of life” as the dependent variable and “age in months” as the underlying time variable. All analyses were further adjusted for parental atopic comorbidities.

Tests for interaction between selected risk factors for AD and preterm or term birth were performed using a log-likelihood ratio test, and subsequent Cox proportional hazard regression analyses were performed stratified by preterm and term birth. Missing data were omitted from the analyses. Analyses were performed with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, CA, USA). The questionnaire was built and managed in the online REDCap (Research Electronic Data Capture) database hosted in the Capital Region of Denmark (17).
at a mean GA of 39.7 ± 1.3 weeks. Median maternal age was 32.4 years (IQR 29.4–36.0) and 32.3 years (IQR 29.8–35.6) for preterm and term children. Median paternal age was 33.4 years (IQR 30.6–37.6) and 33.6 years (IQR 30.7–37.7) for preterm and term children (Table I). In mothers, 77.7% reported being of Scandinavian descent compared with 73.8% of fathers.

Self-reported physician-diagnosed allergy was the most common maternal atopic condition (25.0%), followed by hay fever (15.6%), AD (13.6%) and asthma (13.0%). Paternal atopic conditions included allergy (23.8%), hay fever (18.9%), AD (10.9%) and asthma (17.2%) (Table I).

Prevalence of atopic dermatitis and its characteristics at disease onset

A total of 94 of 440 children (21.4%) were registered with physician-diagnosed AD during the first year of life (Table II). AD was more common in term children (77 of 288) compared with preterm children (17 of 145) (26.7% vs 11.7%, HR 2.5; 95% CI 1.5–4.2; p = 0.001) (Fig. 1a). This remained significant when correcting for GA (HR 2.4; 95% CI 1.5–4.3; p = 0.001) or FLG mutation status (HR 2.5; 95% CI 1.5–4.2; p = 0.001). A dose-dependent association was found between GA and the risk of AD (HR 1.1; 95% CI 1.1–1.2; p = 0.05) and chest (26.7% vs 11.7%, HR 2.5; 95% CI 1.5–4.2; p = 0.001). The median EASI at onset was 0.4 (IQR 0.2–2.4) in term children vs 4.8 (IQR 2.2–7.3) in preterm children (p < 0.0005). In preterm and term children, the most commonly affected skin sites at AD onset were cheeks (35.7% vs 13.7%, p = 0.04), elbows (28.6% vs 47.2%, p = 0.05) and chest (21.4% vs 30.1%, p = 0.5) (Fig. 2).

Filaggrin gene mutation status

In the entire cohort, 7.4% were heterozygous FLG mutation carriers (preterm children 4.1% vs term children 9.2%, p = 0.06). No interaction was found between FLG mutation status and preterm or term birth status (p-value for interaction = 0.4). No homozygous carriers were found. No association was observed between FLG mutations and development of AD (Fig. 1b). A subanalysis restricted to children of Northern and Central European descent did not alter the outcome (n = 351, p = 0.1). No association was observed between FLG mutation status and EASI at AD onset (wild-type, mean EASI: 4.8 ± 4.4; heterozygote, mean EASI: 6.5 ± 2.3; p = 0.6).

**Table II. Prevalence of atopic dermatitis (AD) by childrens’ characteristics, parental comorbidities and pregnancy exposures**

| Prevalence of AD by exposure to variables | Preterm children (AD/all: 17/145) | Term children (AD/all: 77/288) | All children (AD/all: 94/440) |
|-----------------------------------------|-----------------------------------|-------------------------------|-------------------------------|
| Sex                                     | Male                              | Female                        |                                |
| n (%)                                   | 11 (12.5)                         | 43 (25.1)                     | 54 (28.0)                     |
| p-value                                 | 0.457                             |                               |                                |
| Filaggrin gene mutation status          | Wild-type                         | Heterozygote                  |                                |
| n (%)                                   | 16 (11.4)                         | 69 (25.8)                     | 85 (20.9)                     |
| p-value                                 | 0.055                             |                               |                                |
| Birth method                            | Vaginal                           | Caesarean section             |                                |
| n (%)                                   | 6 (11.5)                          | 44 (24.9)                     | 50 (21.8)                     |
| p-value                                 | >0.001                            |                               |                                |
| Season of birth                         | Spring                            | Summer                        |                                |
| n (%)                                   | 4 (13.3)                          | 18 (29.5)                     | 22 (24.2)                     |
| p-value                                 | 0.593                             |                               |                                |
| Preterm                                  | Winter                            |                                |                                |
| n (%)                                   | 2 (14.3)                          |                                |                                |
| p-value                                 | 0.953                             |                               |                                |
| Parental atopic diseases                | Maternal atopic disease (AD, asthma, hay fever or allergy) |                               |                                |
| n (%)                                   | Yes 9 (22.0)                      | 30 (30.6)                     | 39 (28.1)                     |
| p-value                                 | 0.780                             |                               |                                |
| Paternal atopic disease (AD, asthma, hay fever or allergy) | Yes 6 (9.2)                      | 44 (26.5)                     | 50 (21.6)                     |
| p-value                                 | 0.592                             |                               |                                |
| No parents with atopic disease          | One parent with atopic disease    | Both parents with atopic disease |                                |
| n (%)                                   | Yes 8 (17.0)                      | 26 (19.7)                     | 34 (19.0)                     |
| p-value                                 | 0.219                             |                               |                                |
| No                                     | 5 (9.8)                           | 24 (20.5)                     | 29 (17.3)                     |
| p-value                                 | 0.004                             |                               |                                |
| Exposures in pregnancy                  | Indoor painting during pregnancy  |                               |                                |
| n (%)                                   | Yes 5 (20.0)                      | 29 (34.9)                     | 34 (31.5)                     |
| p-value                                 | 0.135                             |                               |                                |
| New floors/carpets during pregnancy     | Yes 2 (50.0)                      | 9 (47.4)                      | 11 (47.8)                     |
| n (%)                                   | No 10 (12.5)                      | 44 (24.6)                     | 54 (20.8)                     |
| p-value                                 | 0.245                             |                               |                                |
| Domestic pet exposure during pregnancy  | Yes 13 (12.7)                     | 64 (26.2)                     | 77 (22.3)                     |
| n (%)                                   | No 13 (18.1)                      | 64 (29.6)                     | 77 (26.7)                     |
| p-value                                 | 0.004                             |                               |                                |
| Domestic dog exposure during pregnancy  | Yes 2 (16.7)                      | 3 (17.6)                      | 5 (17.2)                      |
| n (%)                                   | No 14 (13.8)                      | 72 (27.7)                     | 86 (23.8)                     |
| p-value                                 | 0.015                             |                               |                                |

*Due to missing data, the number of participants may be less than total the sample sizes. Bold numbers are all the significant p-values (<0.5).

Parental risk factors for atopic dermatitis

A paternal history of atopic disease was associated with increased risk of AD in the entire cohort (adjusted HR 1.8; 95% CI 1.1–2.8; p = 0.02), with no significant interaction between preterm and term children (p-value for interaction 0.4).

In preterm children, a family history of atopic disease in both parents was associated with AD (adjusted HR 7.5; 95% CI 2.0–28.1; p = 0.003 (Fig. 1c). In term children, no association was found between both parents having a history of atopic disease and AD (adjusted HR 1.7; 95% CI 0.8–3.3; p = 0.4), but having only one parent with a history of atopic disease was associated with AD (adjusted HR 1.7; 95% CI 1.0–2.9; p = 0.03). No association was found between a parental history of atopic disease and EASI at onset of AD (no parental atopic disease,
mean EASI $3.2 \pm 2.2$; parental atopic disease, mean EASI $5.5 \pm 5.0; p = 0.1$).

**Season of birth as risk factor for atopic dermatitis**

In preterm children, autumn or winter birth was associated with AD (adjusted HR 3.3; 95% CI 1.2–9.2; $p = 0.03$), whereas no association was found in term children (adjusted HR 1.2; 95% CI 0.8–1.8; $p = 0.5$) (Fig. 1d).

**Exposures in pregnancy as risk factors for atopic dermatitis**

In the entire cohort, indoor decorating (painting) during pregnancy was associated with increased risk of AD (adjusted HR 1.5; 95% CI 1.0–2.4; $p = 0.05$). Replacing carpets or installing new flooring during pregnancy was associated with increased risk of AD in the entire cohort (adjusted HR 2.6; 95% CI 1.4–4.9; $p = 0.003$), in preterm (adjusted HR 5.8; 95% CI 1.3–26.6; $p = 0.02$) and term children (adjusted HR 2.1; 95% CI 1.0–4.2; $p = 0.04$), which remained significant when adjusting for parental educational level in the entire cohort (adjusted HR 3.0; 95% CI 1.3–6.6; $p = 0.01$), in preterm children (adjusted HR 12.8; 95% CI 1.6–102.7; $p = 0.02$), but not in term children. No association was found between parental smoking status and AD (maternal smoking $p = 0.9$, paternal smoking $p = 0.2$).

Exposure to domestic pets in pregnancy was associated with lower risk of AD (adjusted HR 0.5; 95% CI 0.2–0.9; $p = 0.02$), but no association was found for exposure to domestic dog or domestic cat separately (dog, adjusted HR 0.6; 95% CI 0.3–1.5; $p = 0.3$ and cat, adjusted HR 0.6; 95% CI 0.6–1.6; $p = 0.3$).

**Emollient application as a risk factor for atopic dermatitis**

In term children, daily application of emollients at 2 months of age was associated with increased risk of AD (adjusted HR 2.9; 95% CI 1.7–5.0; $p < 0.0005)$ (Fig. 1f).
DISCUSSION

This prospective birth cohort study showed, for the first time, that preterm children had a significantly reduced risk of developing AD during the first year of life compared with term children, with a dose-dependent association between risk of AD and GA at birth. Prematurity was associated with older age at AD onset as well as lower AD severity.

Interpretation

While preterm birth has been associated with a decreased risk of AD (11–14), no studies have investigated the possible underlying mechanisms. A lower prevalence of FLG mutations was found in preterm born children compared with term children, probably contributing to the lower risk of developing AD. Several other mechanisms have previously been hypothesized for the lower risk of AD in preterm children (11, 18). Since pregnancy is characterized by a promotion of T helper (Th)2 mediated cytokines, essential for maintaining normal pregnancy and not rejecting the foetus (19), the shorter foetal period of Th2 exposure in preterm children might impact the foetal immune system, thereby reducing the risk of AD (11). Increased antigen penetration through the immature skin barrier or an altered skin microbiome in preterm children could contribute to development of tolerance (11).

Term children developed AD at an earlier age and had a higher EASI score at onset compared with preterm children. However, skin sites affected by AD were essentially similar in the 2 groups. These findings indicate that preterm children with AD may have a milder disease course and delayed onset.

A recent meta-analysis showed that AD was associated with both maternal or paternal history of atopic disease (20). While the current study could not confirm an association between AD and maternal history of atopic disease, we found an association with paternal history of atopic disease. Small study size, along with possible participation and recall bias, may explain the lack of association in term children regarding 2 parents with atopic disease.

Autumn or winter birth has been associated with increased risk of AD in countries in the Northern hemisphere (6). While we could not confirm this association in term children, preterm children had a 3-fold increased risk of AD when born during autumn or winter. This finding suggests that factors leading to dry skin could have a more negative effect on the immature skin barrier in preterm children.

Previous studies showed a reduced risk of developing AD in children exposed to domestic pets in infancy and, in particular, to domestic dogs (8, 21). The current study confirmed the inverse association for domestic pet exposure; however, we were not able to confirm the association specifically for exposure to domestic dogs. It has been suggested that exposure to dogs in infancy results in increased exposures to endotoxins and microbial components, thereby shifting the immune system, promoting Th1-mediated cytokines (22). However, inverse causation cannot be ruled out, since parents with a fear of atopic disorders may choose not to acquire a pet.

Volatile organic compounds (VOC) are thought to be environmental risk factors for AD, and infants living in newly built houses or living with indoor renovation activities have increased risk of developing AD in early childhood (7, 23, 24). Indeed, the current study found an association between exposure to indoor painting or installation of new flooring during pregnancy and development of AD. The mechanisms by which VOCs may cause AD are not known, but VOCs are thought to cause cutaneous oxidative stress, resulting in Th2 polarization in the skin and thereby causing impaired skin barrier and AD (7).

Large recent trials have shown that prophylactic emollient application seems not to prevent development of AD, but, in fact, increase the risk of AD (25, 26). The current study found a positive association between frequent application of emollients reported at 2 months of age and development of AD. While it could be a result of inverse causation, since parents of children with dry skin will tend to apply emollients, the use of emollients at 2 months of age was similar among heterozygote and wild-type FLG mutation carriers.

Strengths and limitations

This prospective study is the first to compare the risk and severity of AD at onset in preterm and term children along with first clinical presentation. A major strength of the current study was the prospective design with several clinical skin examinations, resulting in few children lost to follow-up and a relatively high parental questionnaire response rate. The study was strengthened by the close contact between parents and study personnel, where parents were regularly encouraged to contact the study personnel in case of suspected AD. Nonetheless, we cannot rule out that the current study may have missed incident cases of AD. Moreover, we only assessed the association between risk factors and development of AD during the first year of life, and it is possible that longer follow-up could have changed the outcome. None of the clinical assessments were blinded, potentially introducing bias.

Since all term children were recruited from Copenhagen, the findings of the current study may not be generalized to rural areas in Denmark. Also, parents from more resourceful families and parents with a history of more severe atopic disease could have been more willing to participate in the study, thereby introducing bias (27, 28). We only included twins and triplets in the preterm population and they do not represent the general population.
Premature born children were scheduled to participate in only one follow-up visit, since they continued to have many hospital visits for conditions associated with premature birth after their discharge from hospital. The prevalence of AD and FLG mutations is similar to other studies, indicating that this is not a concern. Adults may not be able to recall if they had atopic diseases in childhood, which potentially introduces misclassification in our analysis on parental heritability (29).

Conclusion
This prospective birth cohort showed that preterm birth was associated with a decreased risk of developing AD during the first year of life, older age at onset and lower AD severity. Overall, this study confirmed previous risk factors for AD and found that the risk factors were essentially the same in preterm and term born children, apart from a lower prevalence of FLG mutations in preterm children.

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