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Atopic dermatitis and birth factors: historical follow up by record linkage

[Paper]

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Abstract

Objective: To study if factors at birth are associated with later development of atopic dermatitis.

Design: Historical follow up by record linkage from Danish medical birth register. Children were followed up for 5.5 to 8.5 years. Second historical follow up study comprising questionnaire to mothers of singleborn children 6.5 to 9.5 years after birth.

Setting: Private dermatology clinics and dermatology and paediatric departments in the municipality of Aarhus, Denmark.

Subjects: 7862 singletons born in hospital between 1 January 1984 and 31 December 1986 to mothers living in the municipality of Aarhus. Questionnaires sent to 985 mothers.

Main outcome measures: Gestational age, birth weight, parity, and age of mother at the time of birth. Atopy in children diagnosed by specialists in dermatology and physicians. Family size; diagnosis of atopic dermatitis, allergic rhinitis, and asthma; family predisposition; and mothers' smoking habits during pregnancy determined from questionnaires.

Results: Of 7862 children, 403 were diagnosed as having atopic dermatitis by a specialist; the cumulative incidence at age 7 was 5.6%. High gestational age and low parity were associated with an increased risk of atopic dermatitis. Among 985 children atopic dermatitis had been diagnosed by any physician in 184; the cumulative

incidence at age 7 was 18.7%. High birth weight, high gestational age, and family history of atopy were associated with increased risk of atopic dermatitis.

Conclusion: In both studies the incidence of atopic dermatitis was associated with high gestational age and in one with high birth weight also. The causes for these associations are at present unknown but may indicate that even during gestation factors associated with atopic dermatitis influence maturation.

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Introduction

Atopic dermatitis is a chronic skin disease of unknown aetiology that is most prevalent in early childhood. [1,2] Recent epidemiological studies have supported an increased incidence of atopic dermatitis. [3-10] Such an increase could simply be due to the fact that more children are seen by doctors. The increase has also been related to environmental factors such as pollution and indoor environment, an increase in respiratory infections, and the ingestion of certain foods. [11-13] So far, however, there has been little evidence to support these suggestions. A British national birth cohort of 5 year olds born in 1970 showed an association with more positive health behavior in parents and in the most advantaged socioeconomic groups, educational level probably being the main factor. [14,15] Recent follow up of a British national birth cohort born in 1958 confirmed an association with a high social class. [16]

In Denmark epidemiological studies of twins have documented an increase in the cumulative incidence of atopic dermatitis at age 7 from 3.2% in 1960-4 to almost 12% in 1979. [17,18] Results have shown that atopic dermatitis is strongly influenced by genetic factors because the concordance rate in monozygotic twins was about 80% compared with about 20% in dizygotic twins. [5,17,18] It is difficult to imagine, however, that changes in the genetics of atopic dermatitis could explain its rapid

increase in many countries during the past 30 years.

During the 1980s the age of first time mothers in Denmark increased. Birth weight has increased with the age of the mother as well as with parity. [19] We investigated the influence of specific birth factors, including the age of the mother, gestational age, and birth weight, on the risk of developing atopic dermatitis. We also examined the influence of hereditary factors, smoking during pregnancy, and season of birth. Unfortunately, the Danish medical birth register has no information on social class of the investigated families.

Subjects and methods

The study cohort included all of the 7862 singleborn children born between 1 January 1984 and 31 December 1986 at the Aarhus Maternity Hospital to mothers living in the municipality of Aarhus. The hospital covers 99% of all births in the municipality. Information about parental age, parity, gestational age, and birth weight was obtained from the Danish medical birth register. Information on deaths and emigration from the region was obtained from the Danish national population register.

The first study included all the children in the cohort, and the diagnostic criterion was a specialist diagnosis of atopic dermatitis. During the summer of 1992 we manually extracted information from the records of the dermatology and paediatric departments and from all the practising dermatologists in Aarhus about all contacts during 1984-92 in which children were diagnosed as having atopic dermatitis. These clinics are free of charge and the only source of specialised services for skin diseases in the municipality. The information was linked to the study cohort file by means of personal identification numbers, and information from the population register was used to identify exclusions (deaths and emigrations from the capture area). The average (range) follow up time

since birth was 6.3 (5.5 to 8.5) years.

The purpose of the second study was to investigate further a hypothesis about a decreased risk of atopic dermatitis in preterm children. In this study the diagnostic criterion was the parents' report of a diagnosis of atopic dermatitis given by any doctor. We used a stratified sample of 1060 children from the same cohort, with an overrepresentation of preterm children (gestational age <37 weeks, 19%). The samples of term (gestational age 37-40 weeks, 54%) and post-term children (gestational >40 weeks, 27%) were matched with the sample of preterm children by sex. Families who had emigrated from Aarhus before data collection as well as families in which the child or mother, or both, had died were excluded. In the summer of 1993 questionnaires were sent to the sample families. The questionnaire included questions on atopic dermatitis in the child, other symptoms of atopy, family history of atopy, and mother's smoking habits during pregnancy. The information was linked to the cohort file by means of personal identification numbers. The average (range) follow up time since birth was 6.8 (6.5 to 9.5) years.

Multiple births were left out of both studies because of the influence on gestational age and birth weight. [20-24] The studies were approved by the ethics committee of the County of Aarhus and by the Danish Data Protection Agency.

Statistical analysis

Children who had died or moved outside the municipality and five neighbouring municipalities during the follow up period were considered censored at the time of death or emigration.

The cumulative incidence of diagnosis of atopic dermatitis was estimated by Kaplan-

Meier's method, and relative risk estimates were obtained by Cox's regression.

Because of the sampling procedure the cohort in the second study was not representative for the entire cohort regarding gestational age and sex distribution, and the estimate of cumulative incidence was adjusted by direct standardisation to the gestational age and sex distribution in the entire cohort.

As gestational age and birth weight are closely correlated, the inclusion of both in a regression analysis gives unstable results that are difficult to interpret. We therefore calculated the expected birth weight according to gestational age and sex from the information in the entire birth cohort and included information on birth weight as the deviation from the expected birth weight in the analysis. The equation obtained by linear regression, expressing birth weight in grams (BW) as a function of sex and gestational age (GA) was: $E(BW) = 32\,027 - 156 \times \text{sex (female)} - 3115.25 \times GA + 98.841 \times GA^2 - 0.96785 \times GA^3$.

The data analysis was performed with SPSS for Windows, version 6.1.3. [\[25\]](#)

Probabilities of <5% were considered significant.

Results

The first study comprised 7862 children. Seventy nine children (mean age 0.7 years) died, 912 (3.7 years) moved out of the study area, and 403 (3.2 years) were diagnosed by specialists as having atopic dermatitis. [Table 1](#) and [Figure 1](#) show the cumulative incidence. The incidence was low in the first year of life, 1.2% a year in 1-2 year old children, and about 0.7% a year in 3-6 year old children. At the age of 7 the cumulative incidence was 5.6%.

	Age (years)							
	1	2	3	4	5	6	7	8
Study 1	0.5	1.7	2.9	3.7	4.3	4.8	5.6	5.9
Study 2*	6.4	11.7	14.3	16.6	17.1	17.8	18.7	19.6

*Standardised to distribution of sex and gestational age in entire study cohort.

Table 1. Cumulative incidence (per 100 children) of diagnosis of atopic dermatitis in both studies

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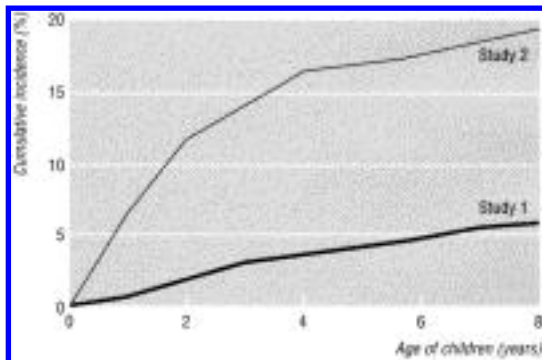


Figure 1. Cumulative incidence of atopic dermatitis among children from 0 to 8 years of age in studies 1 and 2

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In the second study we sent out 1060 questionnaires and received 985 replies, yielding a response rate of 93%, equal in the three gestational age strata (data not shown). The parents of 184 children reported a diagnosis of atopic dermatitis given by a doctor. The cumulative incidence is also shown in [Table 1](#) and [Figure 1](#). The incidence was highest in the first two years of life, about 6% a year, while for 2 to 6 year old children it was 1-2% a year. At the age of 7 the adjusted cumulative incidence was 18.7%.

([Table 2](#)) shows the relative risks associated with birth factors in the first study. The sex of the child and maternal age did not significantly influence the risk of atopic dermatitis, but there was a significant inverse relation with parity. Post-term children had a significantly increased risk for later development of atopic dermatitis, but there was an insignificantly decreased risk for preterm children. There was a weakly insignificant relation with birth weight when we controlled for gestational age and sex.

Predictor variable	No. of subjects (n=265)	No. with diagnosis (n=85)	Unadjusted Relative risk (95% CI)	P value	Adjusted Relative risk (95% CI)	P value
Sex of child						
Boy	140	50	1.00	0.78	1.00	0.78
Girl	125	35	1.19 (0.69 to 2.02)		1.00 (0.58 to 1.72)	
Maternal age at childbirth (years)						
<20	20	10	1.00	0.95	1.00	0.95
20-24	100	40	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
25-29	100	35	1.10 (0.67 to 1.80)		1.00 (0.60 to 1.70)	
≥30	45	10	1.00 (0.40 to 2.50)		1.00 (0.40 to 2.50)	
Parity						
1	40	20	1.00	0.82	1.00	0.82
2	100	40	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
3	100	35	1.10 (0.67 to 1.80)		1.00 (0.60 to 1.70)	
≥4	25	10	1.00 (0.40 to 2.50)		1.00 (0.40 to 2.50)	
Gestational age (weeks)						
<36	100	40	1.00 (0.60 to 1.65)	0.00	1.00 (0.60 to 1.65)	0.00
36-37	100	35	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
≥38	65	10	1.00	0.80	1.00	0.80
Weight (kg)						
<3.5	100	40	1.00 (0.60 to 1.65)	0.00	1.00 (0.60 to 1.65)	0.00
3.5-4.5	100	35	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
≥4.5	65	10	1.00	0.80	1.00	0.80
Weight (kg) expected from weight gain						
<3.5	100	40	1.00 (0.60 to 1.65)	0.00	1.00 (0.60 to 1.65)	0.00
3.5-4.5	100	35	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
≥4.5	65	10	1.00	0.80	1.00	0.80
Sex of mother						
Male	100	40	1.00 (0.60 to 1.65)	0.00	1.00 (0.60 to 1.65)	0.00
Female	165	45	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	

Table 2. Predictors of specialist diagnosis of atopic dermatitis according to birth factors (Cox's regression analysis) in first study

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(Table 3) shows the relative risk associated with birth factors in the second study. The risk was highest for girls (not significant), and there was no relation with maternal age and parity. There was a significant association with gestational age, with the highest risk among post-term children. Furthermore, there was a significantly increased risk for children with high birth weight compared with expected weight for sex and gestational age. The increased risk for "heavy for dates" children was present in all gestational age strata (data not shown).

Predictor variable	No. of subjects (n=265)	No. with diagnosis (n=85)	Unadjusted Relative risk (95% CI)	P value	Adjusted Relative risk (95% CI)	P value
Sex of child						
Boy	140	50	1.00	0.78	1.00	0.78
Girl	125	35	1.19 (0.69 to 2.02)		1.00 (0.58 to 1.72)	
Maternal age at childbirth (years)						
<20	20	10	1.00	0.95	1.00	0.95
20-24	100	40	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
25-29	100	35	1.10 (0.67 to 1.80)		1.00 (0.60 to 1.70)	
≥30	45	10	1.00 (0.40 to 2.50)		1.00 (0.40 to 2.50)	
Parity						
1	40	20	1.00	0.82	1.00	0.82
2	100	40	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
3	100	35	1.10 (0.67 to 1.80)		1.00 (0.60 to 1.70)	
≥4	25	10	1.00 (0.40 to 2.50)		1.00 (0.40 to 2.50)	
Gestational age (weeks)						
<36	100	40	1.00 (0.60 to 1.65)	0.00	1.00 (0.60 to 1.65)	0.00
36-37	100	35	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
≥38	65	10	1.00	0.80	1.00	0.80
Weight (kg)						
<3.5	100	40	1.00 (0.60 to 1.65)	0.00	1.00 (0.60 to 1.65)	0.00
3.5-4.5	100	35	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
≥4.5	65	10	1.00	0.80	1.00	0.80
Weight (kg) expected from weight gain						
<3.5	100	40	1.00 (0.60 to 1.65)	0.00	1.00 (0.60 to 1.65)	0.00
3.5-4.5	100	35	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	
≥4.5	65	10	1.00	0.80	1.00	0.80
Sex of mother						
Male	100	40	1.00 (0.60 to 1.65)	0.00	1.00 (0.60 to 1.65)	0.00
Female	165	45	1.00 (0.60 to 1.65)		1.00 (0.60 to 1.65)	

Table 3. Predictors of doctor diagnosis of atopic dermatitis (reported by parents) according to birth factors (Cox's regression analysis) in second study

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(Table 4) shows the relative risks associated with family history of allergic disease. The

risk was positively associated with all variables, especially atopic dermatitis among the parents. Maternal smoking during pregnancy did not affect the risk of atopic dermatitis.

Variables	Study 1		Study 2	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Atopic dermatitis in parents	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.001		0.001	
Maternal smoking during pregnancy	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.85		0.85	
Paternal smoking during pregnancy	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.85		0.85	
Maternal atopy	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.001		0.001	
Paternal atopy	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.001		0.001	
Maternal hay fever	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.001		0.001	
Paternal hay fever	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.001		0.001	
Maternal asthma	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.001		0.001	
Paternal asthma	1.0		1.0	
Yes	1.0		1.0	
No	1.0		1.0	
P value	0.001		0.001	

Table 4. Predictors of doctor diagnosis of atopic dermatitis (reported by parents) according to family history (Cox's regression analysis)

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We did not find any relation between year of birth or month or season of birth and risk in either study (data not shown).

Discussion

Atopic dermatitis is strongly associated with genetic factors as documented in previous and present studies. [5,17,18] Genetic factors cannot explain the rapidly increasing incidence, [17] so we looked at various birth factors and their possible relation to later expression of atopic dermatitis.

The two studies reported here gave essentially the same results concerning the effect of gestational age: a significantly increased risk of developing atopic dermatitis among post-term children. The effect of birth weight was different in the two studies, with no association in the first, whereas the "heavy for dates" children in the second study had a significantly increased risk of atopic dermatitis. The difference might be explained by the fact that the definition of atopic dermatitis was different in the two studies. We conclude that the risk of developing atopic dermatitis is increased for children born

post-term ($\geq$ to 41 weeks' gestation) and possibly decreased for children born preterm. A lack of association between atopic dermatitis and preterm birth, however, has previously been shown. [26] There may also be an independent relation, with birth weight in children born "heavy for dates" having an increased risk of developing atopic dermatitis.

In the second study we studied preterm birth and atopic dermatitis. The sampling principle for this study was somewhat complex by matching the term and post-term samples to the preterm sample by sex. This gave rise to an overrepresentation of preterm children and of boys in all gestational groups. For estimating the overall incidence we standardised the raw estimates to the sex and gestational distribution of the entire cohort. The skewed sample does not introduce bias in the relative risk estimates.

We believe that any selection bias in the second study would probably lead to an overestimate of the overall incidence because of less interest among parents of children without allergic problems. With a participation rate of 93% in all gestational groups, however, selection bias is unlikely to have affected the estimates of overall incidence and relative risk substantially.

The Danish medical birth register is remarkably complete: information on birth weight was missing in only 0.1% and information on gestational age in 0.3% of the children in the cohort. In Denmark, health care is provided free of charge for all permanent residents. Prenatal care is provided by general practitioners and midwives, who predict the date of birth based on the date of the last menstruation. If the gestational age is uncertain, an ultrasound scan may be carried out. Thus, determination of gestational age is as accurate as possible. While measuring birth weight is simple, gestational age

may be subject to misclassification. [27] It is unlikely, however, that any misclassification of gestation should be differential, and the same pattern of effect of birth weight was found in all gestational groups in both studies.

Estimates of incidence 🏠

The two studies gave rise to very different estimates of incidence. This was expected as only a fraction of children with atopic dermatitis are examined by specialists. The incidence estimate from the first study reflects the incidence of severe cases but is no doubt also influenced by iatrogenic factors—for example, parental anxiety. Iatrogenic here refers to the combination of factors that causes parents to bring a child to a doctor. The incidence estimate from the second study probably includes some false positive diagnoses because of overdiagnosis by general practitioners and by the parents mistaking a diagnosis of unspecific dermatitis for atopic dermatitis. On the other hand, false negative diagnoses can no doubt also occur; some mild cases remained undiagnosed or were not recalled. The "true" incidence of a disease like atopic dermatitis cannot be established in studies like ours, and even conceptually it is difficult to distinguish the mildest cases from non-cases.

The observation in the first study of a decreased incidence of atopic dermatitis with parity could reflect the fact that the first child is more likely to develop atopic dermatitis. In a British study hay fever was reported to be inversely related to the number of children in the household. The same pattern was observed for eczema in infancy. [28] Similar gradients in hay fever and eczema with increasing family size were reported at 5 years of age among British children born in 1970. [29] In Denmark average parity did not change essentially during the 1980s. There has been some shifting of parity in different age groups of mothers—that is, first birth has become more common in mothers between 25 and 34 years of age. [19] One could imagine

that family size and the age of the mother are dependent on socioeconomic class of the families. In our research we could not take socioeconomic class into consideration. The relative risk estimates, however, may have been subject to information bias because of iatrotropic factors. It is difficult to explain the discrepancy in our results regarding parity. We tend to believe that the decreased incidence of atopic dermatitis with increasing parity in the first but not the second study reflects iatrotropic factors (parental anxiety is highest for the first child) rather than a real difference in incidence.

Physiology of dermatitis🏠

Atopic dermatitis is somehow linked to a disturbance of the T lymphocyte system. We have previously provided experimental evidence that T lymphocytes in the skin of patients with atopic dermatitis differ in vitro from normal T cells in that they can show cytokine driven growth. [30,31] Our findings provide only circumstantial evidence for possible abnormal maturation of T cells as a central pathophysiological event leading to the development of atopic dermatitis. Our studies of continuous T cell lines established from the skin of patients with atopic dermatitis, however, may be indicators of abnormally mature or immature T lymphocytes.

T lymphocytes mature in the thymus, which contains epithelium from ectodermal tissue. [32] We suggest that a disturbance in the "communication" between epithelium in the thymus and maturing T lymphocytes could lead to an inadequate T lymphocytes selection in the thymus. [33] It is known from studies in mice that about 98% of all pro-T lymphocytes are removed in the thymus through positive or negative selection. We imagine that a defect in this selection process leads to the emission of too many T lymphocytes, which then collect in the skin. This disturbance could be graded so a near complete T lymphocyte selection would lead to mild atopic dermatitis of short duration

whereas a more pronounced disturbance would lead to more severe and long lasting atopic dermatitis. The genetic defect could be associated with the ectodermal tissue. If such a genetically determined "ectodermal dysmaturational" is expressed in utero this could be a cause for prolonged gestation.

In conclusion, two studies of a cohort of 7862 single-born births provide evidence for an association between prolonged gestational age and later development of atopic dermatitis. There also seems to be an independent association between "heavy for dates" children in all gestational age groups and atopic dermatitis in children with milder eczema. The causes for these associations, which point towards factors already changing gestation, are at present unknown.

Key messages

- This Danish study found that the cumulative incidence of atopic dermatitis at the age of 7 years was 18.7% in 1993
- Children born after term had a significantly increased risk of developing atopic dermatitis
- Children whose birth weight was high for their sex and gestational age also had an increased risk of developing atopic dermatitis
- These findings suggest that a genetically determined predisposition to developing atopic dermatitis is expressed in utero

ABO and ARE contributed equally to this work. We thank Drs Hans Afzelius, Jorgen V Christiansen, Lars Henriksen, Poul Olholm Larsen, and Ole Gowertz Rasmussen for their cooperation in supplying information about patients seen in their clinics. We

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Conflict of interest: None.

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