

Risk analysis of early childhood eczema

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Background: The increasing prevalence of eczema suggests the role of environmental factors triggering a genetic predisposition. **Objective:** To analyze the effect of environmental exposures in early life and genetic predisposition on the development of eczema before age 3 years.

Methods: The Copenhagen Study on Asthma in Childhood is a prospective clinical study of a birth cohort of 411 children born of mothers with asthma. Eczema was diagnosed, treated, and monitored at the clinical research unit, and complete follow-up for the first 3 years of life was available for 356 children. Risk assessments included filaggrin loss-of-function mutation; parent's atopic disease; sex; social status; previous deliveries; third trimester complications and exposures; anthropometrics at birth; month of birth; duration solely breast-fed; introduction of egg, cow's milk, and fish; time spent in day care; cat and dog at home; feather pillow; nicotine in infant's hair; and temperature and humidity in bedroom.

Results: Eczema developed in 43.5% of the infants. Filaggrin mutation (odds ratio [OR], 3.20; 95% CI, 1.46-7.02; $P = .004$), mother's eczema (OR, 2.80; 95% CI, 1.70-4.63; $P < .0001$), and father's allergic rhinitis (OR, 1.91; 95% CI, 1.09-3.33; $P = .02$) were directly associated with risk of eczema. Risk of eczema was significantly reduced by birth length (OR per cm increase, 0.87;

95% CI, 0.78-0.97; $P = .02$), increased bedroom temperature (probably inverse causality; OR, 0.80; 95% CI, 0.66-0.97; $P = .02$), and dog living in the home (OR, 0.44; 95% CI, 0.23-0.87; $P = .02$). **Conclusions:** Dog exposure reduced the risk of eczema, whereas short length at birth, filaggrin mutation, and parental atopy increased the risk of eczema by age 3 years. (*J Allergy Clin Immunol* 2009;123:1355-60.)

Key words: Length at birth, breast-feeding, dog, eczema, filaggrin, risk factor

The cumulative incidence of eczema (atopic dermatitis) for young children in Denmark increased 4-fold to 6-fold since the 1960s to a reported prevalence of 15% to 18% in the 1990s,^{1,2} and apparently it is still increasing,³ which suggests an environmental influence on disease expression. Eczema usually presents in the first year of life.^{4,5} Therefore, environmental factors triggering a genetic predisposition should be sought in the perinatal period.

There is a paucity of clinical studies of the development of eczema in infancy. Available reports have classified eczema from symptom questionnaires, a history of community doctors' diagnoses, or cross-sectional observations.⁶⁻⁹ However, the clinical course is capricious, and morphology is instrumental to the diagnosis of eczema, which is based on a syndrome of clinical criteria. Particularly in early age, there is a large interobserver variation and corresponding risk of misclassification.¹⁰ Furthermore, existing reports are of limited sample size, with incomplete follow-up or small numbers of confounder assessments.

The Copenhagen Prospective Study on Asthma in Childhood (COPSAC) is a birth cohort monitored, diagnosed, and treated prospectively for eczema and related atopic diseases exclusively by the COPSAC clinical research unit, providing detailed data on the clinical expression of atopic phenotypes. The progressively changing predilection skin lesion pattern of eczema during the first 3 years of life in the COPSAC cohort has been reported.⁴ In addition, COPSAC provides comprehensive assessments of the perinatal milieu, aiming to elucidate critical factors driving disease expression.

We recently discovered that loss-of-function variants in the gene encoding filaggrin (FLG) are major determinants of eczema,^{11,12} which was replicated in several later studies.^{13,14}

Subsequently we demonstrated a significant interaction between FLG loss-of-function main mutations and cat ownership at birth on the development of eczema before age 1 year; dog exposure was moderately protective, but not related to FLG genotype.¹⁵

This article is based on a more comprehensive analysis of the association of 40 potential risk factors (including dog and cat exposures as well as FLG genotype) with eczema presenting by 3 years of age. Measured confounders were adjusted for while estimating effects of these variables on risk of eczema, because a subset of the 40 variables showing at least moderate association with eczema were fit in a model simultaneously.

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Abbreviations used

COPSAC: Copenhagen Prospective Study on Asthma in Childhood
 FLG: Filaggrin
 OR: Odds ratio

METHODS**Subjects**

The COPSAC recruited a birth cohort of 411 children from August 1998 to December 2001. The target population of the study was defined as healthy newborns (>36 gestational weeks) of mothers with a history of doctor-diagnosed asthma. Oral and written informed consent was obtained from all parents of participating children. The study followed the guiding principles of the Declaration of Helsinki and was approved by the Ethics Committee for Copenhagen (KF 01-289/96) and the Danish Data Protection Agency (2008-41-1754). History was recorded online during visits to the COPSAC clinical research unit. Objective measurements were double-checked against source data and the database subsequently locked and tracked by an audit trail.

The participants followed scheduled visits every 6 months and visited the clinic for any acute skin manifestations. The parents were told to note all skin diagnoses and use of medication prospectively between visits. The families used the clinical research unit (not the family practitioner) for diagnosis and treatment of any atopy-related symptoms.

The infants were given a standardized physical examination, and history was obtained by the doctors at the clinical research unit using structured questions and closed response categories including skin manifestations, medication use, healthcare use, lifestyle, and home environment. Eczema was diagnosed according to the criteria of Hanifin and Rajka.¹⁶ The severity of eczema was scored using the Scoring Atopic Dermatitis index (SCORAD).¹⁷

Children were treated according to a predefined written standard operating procedure. Eczema was primarily treated with moisturizer and topical steroids, mainly hydrocortisone.

Sensitization was determined in the children at age ½, 1½, and 4 years by a screening method (ImmunoCAP Phadiatop Infant; Pharmacia Diagnostics AB, Uppsala, Sweden) as well as specific IgE against the most common food and inhalant allergens. Values of the screening method ≥ 0.35 kU/L were considered indicative of sensitization¹⁸ and were analyzed as a dichotomized measurement. Sensitization was determined in the parents also.

Risk assessments

Genotyping for R501X and 2282del4 was performed as previously described.¹¹ Children with either (or both) variants were classified as having the mutant allele.

Genetic predisposition included information on parental history of eczema, allergic rhinitis, and asthma.

Demographics were described by sex, race, and season of birth as well as gestational age, head circumference, and length and weight at birth, the latter supported by midwives' notes. Socioeconomics were evaluated from household income classified into 3 groups, and the highest educational level of parents divided into 3 categories: elementary or middle school, college, and university. Occupational status was described in 4 groups—professionals, nonprofessionals, unemployed and students—based on DISCO classification and ISCO-88 (International Standard Classification of Occupations; International Labour Organization, <http://www.ilo.org>).¹⁹

Pregnancy was described by number of previous deliveries, complications, and exposures. Pregnancy complications during the third trimester were described by occurrence of preterm contractions, pre-eclampsia, pneumonia, or influenza; mother's asthma status (worse, same, better); mode of delivery (cesarean section, vacuum, natural birth); and Apgar score (9-10 or <9).

Exposures during the third trimester were composed of information on smoking, alcohol, medications (oral antibiotics and paracetamol), and physical exercise (0, 1, and >1 time per week).

Postnatal exposures

Cat and dog in the home around time of birth was assessed at the 1-month visit and defined as cat or dog living in the house at birth. Information on the period the child was solely breast-fed; age at introduction of egg, cow's milk, and fish; use of feather pillow; and age at which the child started day care with other children was assessed at every 6-month visit.

Objective assessments of airborne exposures

Nicotine concentration was measured in hair sampled by age 1 year.²⁰

Indoor humidity and temperature were measured simultaneously in the children's bedrooms using a HOBO H8 RH/Temp Logger (Onset Computer Corp, Bourne, Mass; <http://www.onsetcomp.com>). Measurements were logged every 10 minutes for a 4-week period within the first 2 years of life.

Statistical analysis

Simple logistic regression was performed for eczema at 3 years (yes/no) for each of the 40 predictor variables. For the multiple logistic regression, the following basic steps were used to achieve a final model: (i) missing values were first imputed for incomplete variables; (ii) a stepwise selection process was used to include variables into the model in successive blocks; (iii) steps i and ii were repeated for a total of 5 imputed data sets and 5 model fits; (iv) variables selected in at least 4 out of 5 models were then refit in a multiple logistic regression model (without using stepwise selection); (v) step iv was repeated for each of the 5 imputed data sets; (vi) composite estimates and standard errors were determined by combining results from the 5 models. (The SEs of the estimates accounted for the uncertainty caused by imputation of data.) See this article's Online Repository (Statistical Analyses section) at www.jacionline.org for additional details of the statistical modeling.

The Markov Chain Monte Carlo method was used to impute values.²¹ Continuous variables were either log-transformed (if right-skewed) or left unchanged before the imputation analysis. Missing data for variables (either continuous or categorical) were imputed by using multivariate normal theory, as described by Bernaards et al.²²

Blocks of variables were tested successively as follows: heredity (6 variables), social status (3 variables), preconception (3 variables), prenatal (10 variables), birth (7 variables), and postnatal (11 variables). Each variable within a group was tested using the following criteria: $P < .15$ for entry and $P < .20$ to stay. If a variable was entered and remained in the model when its block was tested, this variable was then forced to remain in the model when subsequent blocks were tested, which allowed for the possibility that $P > .2$ for some variables in the final model.

For sets of analyses involving numerous models, the false discovery rate procedure was used with a false discovery rate of 0.05.²³

RESULTS**Descriptive statistics**

The birth cohort included 411 infants born to mothers from Greater Copenhagen, all with a history of asthma (Online Repository, Methods) as previously described in detail.^{19,24-26} A total of 356 (183 girls and 173 boys) had complete clinical follow-up for the first 3 years of life. Reasons for withdrawal included death from sudden infant death syndrome (1 infant), family moved, refusal by parents to continue in the study, or missing a scheduled visit. Descriptive statistics for 40 risk factors analyzed for association with eczema is presented in this article's Tables E1 and E2 in the Online Repository at www.jacionline.org.

Predictors of eczema

For the 40 predictor variables fit with simple logistic regression models, 10 reached statistical significance at the $\alpha=0.05$ level (see this article's Table E3 and E4 in the Online Repository at

TABLE I. ORs for development of eczema by 3 years of age using multiple logistic regression*

Variable	Comparison	Multiple regression		Simple regression	
		OR (95% CI)	P value	OR (95% CI)	P value
Mother's eczema	Yes vs no	2.80 (1.70-4.63)	<.0001	3.10 (2.00-4.79)	<.0001
Father's rhinitis	Yes vs no	1.91 (1.09-3.33)	.02	1.83 (1.16-2.88)	.01
Filaggrin mutations	Yes vs no	3.20 (1.46-7.02)	.004	2.43 (1.23-4.79)	.01
Mother's work	Student vs nonprofessional	0.97 (0.40-2.34)	.94†	1.13 (0.54-2.36)	.75†
	Unemployed vs nonprofessional	2.93 (1.16-7.41)	.02†	2.32 (1.07-5.04)	.03†
	Professional vs nonprofessional	1.17 (0.65-2.11)	.59†	1.33 (0.82-2.16)	.24†
Alcohol, 3rd trimester	Yes vs no	1.88 (0.94-3.75)	.07	1.74 (1.00-3.05)	.05
Exercise per week 3rd trimester	Once vs none	1.44 (0.62-3.36)	.34†	1.87 (0.90-3.88)	.09†
	More than once vs none	0.55 (0.15-1.94)	.26†	0.56 (0.24-1.29)	.17†
Length	Centimeter increase	0.87 (0.78-0.97)	.01	0.90 (0.82-0.99)	.03
Dog at home	Yes vs no	0.44 (0.23-0.87)	.02	0.37 (0.20-0.67)	.001
Time solely breast-fed	Exposure-year increase	2.80 (0.87-9.03)	.10	2.76 (1.01-7.56)	.05
Temperature first year	1°C increase	0.80 (0.66-0.97)	.02	0.77 (0.66-0.91)	.002

*See Statistical Analysis for details on model fitting. For comparison, ORs for simple regression models are given at the right.

†Denotes a comparison of 2 levels within a categorical variable. P values for categorical variables (as a whole): mother's work, P = .19 for simple regression and P = .10 for multiple regression; physical exercise, P = .06 for simple regression and P = .05 for multiple regression.

www.jacionline.org). Presence of filaggrin gene mutations, mother's eczema, father's asthma and rhinitis, third-trimester alcohol use, and longer duration of sole breast-feeding were risk factors for eczema development, whereas increases in bedroom temperature, nicotine in hair, presence of dog at birth, and increased baby length were protective from eczema development. After applying the false discovery rate procedure and using a false discovery rate of 0.05, only filaggrin gene mutations, mother's eczema, dog at home at birth, and temperature remained significant among the original 10 that were significant.

In the multiple logistic regression model, 10 of the 40 predictor variables were included on the basis of selection criteria described in the **Methods**. The significance of predictors in this model decreased slightly relative to univariable models (**Table I**), which may be at least partially explained by collinearity of predictors. However, the results show general consistency between odds ratios (ORs) from the univariable and multivariable models. Mother's eczema (OR, 2.80; 95% CI, 1.70-4.63; $P < .0001$) and the filaggrin gene mutations (OR, 3.20; 95% CI, 1.46-7.02; $P = .004$) were the most significant factors in predicting eczema at 3 years.

Dog at home, baby's length at birth, and bedroom temperature were also significant factors predicting eczema by 3 years of age. Families with dogs had approximately half the odds of developing eczema (OR, 0.44; 95% CI, 0.23-0.87; $P = .02$). Increased length at birth (OR per cm increase: 0.87; 95% CI, 0.78-0.97; $P = .01$) and increased bedroom temperature (OR per 1°C increase: 0.80; 95% CI, 0.66-0.97; $P = .02$) were also associated with reduced risk of eczema. Longer duration solely breast-fed and third-trimester alcohol use were found to be marginally significant risk factors for eczema development ($P = .10$ and $.07$, respectively). **Fig 1** displays a forest plot of predictors in the multivariable model.

Possible selection because of parents' allergy

Homes with parents allergic to dog may be less likely to own a dog, even before the child is born, causing a false association between dog exposure and atopic risk in the baby. We therefore performed a subanalysis estimating the eczema rate stratified for parents' sensitization. In homes of parents sensitized to dog, the eczema rate was 38% if a dog was present at birth and 55% if there was no dog. Likewise, among parents without dog sensitization, the eczema rate was 18% if a dog was present at birth and 47% if

there was no dog. These data demonstrate that even within dog allergy strata, rates of eczema were lower for those who owned a dog compared with those who did not. Running a logistic regression for eczema at 3 years of age as a function of dog ownership and dog allergy yields an OR of 0.311 for the dog effect ($P = .0004$) and 1.485 for the dog allergy effect ($P = .09$). In the model without dog allergy, the OR for the dog effect is 0.291 ($P = .0002$). (When not restricting the data because of missing dog allergy information, the OR for the dog exposure effect is 0.37 [$P = .001$].) Thus, there is no indication of strong confounding by parents' allergy to dog. When this process is repeated with the full multivariable logistic regression model (ie, adding parents' dog allergy variable to the model with 10 predictors, including dog exposure), similar results are observed.

Atopic eczema

Of the 356 subjects in the study, 321 of them had gone through testing for sensitization. Within these 321 subjects, 134 (42%) developed eczema, and 29 (21.6%) of the 134 subjects were sensitized. In the noneczema group, 24 (12.8%) of 187 were sensitized. None of the children was sensitized to dog before the diagnosis of eczema. In 2 infants, the sequence could not be determined because eczema was diagnosed after a negative test but before a subsequent positive test for sensitization.

A subset analysis was performed to explore the relationship between sensitized and nonsensitized phenotypes within those that developed eczema by 3 years of age. Sensitization was tested at 3 time points in early childhood ($\frac{1}{2}$, $1\frac{1}{2}$, and 4 years). A subject was considered sensitized with a positive test result on at least 1 time point. Of the 40 variables tested, only the duration of cow's milk in the diet was found to be significant in differentiating the sensitized and nonsensitized children with eczema. However, this 1 marginal significance does not hold up when applying the false discovery rate of 0.05.

DISCUSSION

Main findings

Dog exposure around birth halved the risk of development of eczema during the first 3 years of life (OR, 0.44; 95% CI, 0.23-

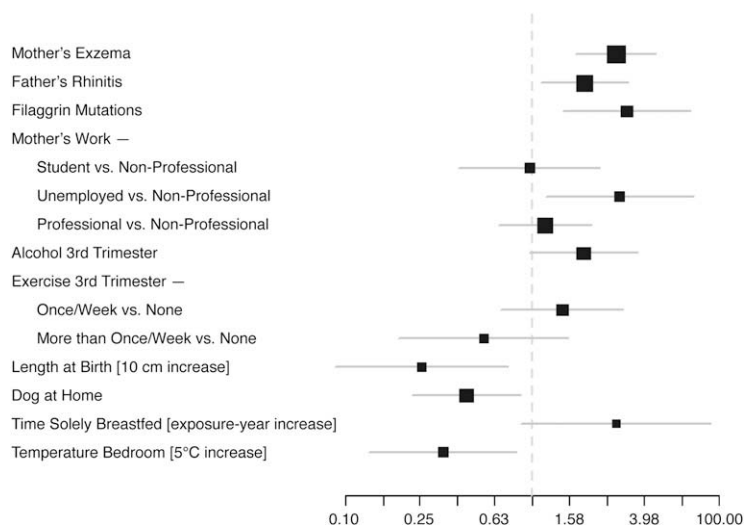


FIG 1. Forest plot of ORs and 95% CIs for predictors of development of eczema by 3 years of age based on multiple logistic regression. (See Statistical Analysis for details on model fitting.) Variables that are risk factors for eczema are greater than 1; those that are protective are less than 1. The box sizes are inversely proportional to the variances of the associated estimators.

0.87; $P = .02$), and this effect was independent of parents' allergy to dog, ruling out inverse causality.

FLG mutation and parental atopy significantly increased the risk of eczema in early childhood. Length at birth and bedroom temperature were the only other measures significantly associated with risk of eczema, both showing an inverse association. However, we interpret the bedroom temperature effect as a case of inverse causation.

Breast-feeding and mother's intake of alcohol during the third trimester seemed to increase the risk of eczema, but the effects were only borderline significant in both the univariable and multivariable analyses.

No associations were seen with sex, race, social status, previous deliveries, third-trimester complications (preterm contractions, pre-eclampsia, pneumonia, influenza, Apgar score, mode of delivery, and mother's asthma status), third-trimester exposures (mother's smoking, antibiotics, paracetamol, and physical exercise), anthropometrics of the newborn, birth month, diet (age at introduction of egg, cow's milk, and fish), age starting day care, cat at home, feather pillow, environmental tobacco exposure, and humidity in bedroom.

There was no difference between atopic (sensitized) and nonatopic eczema in any of the 40 predictor variables evaluated after adjusting for multiple comparisons, arguing against the relevance of such a particular phenotype of eczema with or without concurrent sensitization.

Strengths and limitations of the study

The major strength of our study is the meticulous prospective clinical monitoring, diagnosing, and treating of eczema through the first 3 years of life together with the accurate exposure assessments.²⁷ The cohort was seen regularly at 6-month intervals as well as for acute skin manifestations by the same doctors in the COPSAC clinic, who controlled diagnosis and treatment according to predefined algorithms—that is, diagnoses and treatments were not made by doctors outside our research

unit during this prospective clinical follow-up. The prospective clinical follow-up is the key difference from other cohort studies of eczema, which are mainly based on questionnaires and parents' history of diagnoses made by doctors in the community.⁶⁻⁹

The cumulative incidence of the most common differential diagnosis of seborrheic dermatitis capitis was similar in children with eczema and in children without an eczema diagnosis.⁴ This mitigates against seborrheic dermatitis capitis being mistakenly diagnosed as eczema and confirms the high specificity of eczema diagnosis.

The vigorous confounder assessments reinforce the analyses. Objective assessments included measurements of nicotine in the hair of the child, reflecting long-term exposure of environmental tobacco exposure²⁰ as well as long-term logging of temperature and humidity in the child's bedroom. Perinatal data were collected from midwives' notes. Exposures assessed by history were updated at clinic visits every 6 months by clinical interviews standardized with closed response categories.

The limitations of the study relate to external validity because of the high-risk nature of the cohort. All children were born of mothers with a history of asthma, predominantly of white race, and the conclusions of the study need replication in unselected populations.

We used multiple regression analyses of the cumulated incidence of eczema by age 3 years not accounting for the time order—that is, including data on exposures that may have occurred after disease onset. This approach (as opposed to survival analyses) was necessitated by the large number of variables analyzed. Also, although 40 variables were included in the analysis, there is the potential that unmeasured confounders could still play a role in the observed results.

Multivariable logistic regression analysis was performed in addition to simple logistic regression to find a set of variables that collectively predict eczema at 3 years. Because predictors were fit simultaneously, the effect of any 1 predictor was adjusted for the other predictors in the model, minimizing effects of confounders on the results. However, the consistency of results between the

multivariable and univariable models suggests that there were no major confounders. Here we take a conservative approach and report the primary results as those from the multivariable model. However, one could argue that the univariable results are meaningful in the absence of confounders, which is why they are also presented.

Hosmer-Lemeshow statistics indicated strong goodness-of-fit across the logistic regression models, including the multivariable model ($P > .3$ across fit multivariable models for 5 imputed data sets). The use of imputation was important in the multivariable analysis to make complete records and boost power for the analysis. The uncertainty caused by imputing values was accounted for in the final estimates.

The conclusions of the study are limited by the power of the study. Because of the comprehensive clinical follow-up, the number of subjects included was limited at 356. This is particularly a concern for the risk variables showing borderline significance. Length of solely breast-feeding and mother's use of alcohol only showed such borderline significance, which may be a result of the power of our statistical approach and the limited number of subjects.

Possible explanations of the findings

We recently discovered the filaggrin mutation to be such a strong determinant of eczema in COPSAC¹¹ and replicated this finding in a population-based study.¹² In the current analyses, we confirm a 3-fold increased risk from filaggrin mutation after confounder adjustment. Still, mother's eczema and father's allergic rhinitis remained strong risk factors beyond the filaggrin mutation, confirming the role of other genetic mutations. Notably, our analyses show a strong heritability from mother's eczema and none from father's eczema. This suggests a stronger penetrance of maternal than paternal eczema, although it may be confounded from the selection of mothers with asthma.

Despite this very strong heritability of eczema, the increasing prevalence in recent decades suggests a strong environmental influence. Recently, we demonstrated a significant interaction between FLG loss-of-function main mutations and cat ownership at birth on the development of early-life eczema. Cat exposure at birth substantially increased the risk of eczema within the first year of life in children with FLG loss-of-function variants, but not among those without. Dog exposure was protective independent of FLG genotype, and we replicated this observation in a birth cohort from the United Kingdom.¹⁵ The current study confirms a robust protective effect from perinatal exposure to dog in the home after comprehensive confounder adjustment. A recent systematic review of the evidence for a role of furry pets in eczema found no clear evidence that early pet exposure is associated with increased risks of subsequent eczema, and suggested that avoidance behavior in high-risk families could explain such findings (inverse causality).²⁸ However, none of the studies reviewed accounted for FLG mutation and the interaction between cat exposure and FLG mutation recently demonstrated.¹⁵ It seems unlikely that avoidance behavior explains these observations in our study of protection from dog inasmuch as cat was found to be a risk factor in the same study. Importantly, in our study, we documented cat or dog exposure from birth (ie, before eczema occurrence), thus eliminating the uncertainty of the direction of association between exposure and disease. In particular, the effects of dog and cat exposures were not

prone to inverse causality from symptom development in the child because the indicator was presence at birth. Avoidance behavior on behalf of the parent was accounted for by including parents' allergic rhinitis, eczema, and asthma in the model. In addition, we incorporated parents' specific allergy to dogs, which did not mitigate the observed dog effect. In particular, there were no material changes when an indicator variable for dog sensitization (for either mother or father or both) was added to the final multivariable model. It is therefore unlikely that the protective effect of dog is caused by parents avoiding dog because of allergy.

We assessed only animals living in the household, although other exposures outside the home may be relevant, but this would only have biased the risk estimates toward the null, potentially underestimating the true risk.

The mechanism by which exposure to dogs around birth protects against eczema is unknown. Specific IgE would not be expected to be involved inasmuch as the effect is protective, and indeed, specific IgE was not present before eczema in exposed children. This suggests that dog exposure may act through other mechanisms than specific IgE, or it may be a surrogate marker for other unknown environmental influences. Early colonization of airways with pathogenic bacteria was recently shown to be a significant determinant of the development of childhood asthma and raised total IgE.²⁵ In analogy with this observation, we speculate that the particular microbiology carried by pets may be mediating their effect on disease expression. Alternatively, having dog is a surrogate measure of other particular lifestyle factors, which needs to be explored in future studies.

The finding of an association between higher temperature in bedroom and a lower risk of eczema is probably an example of inverse causality. The temperature was determined at age 1 year, after debut of the majority of eczema cases—that is, parents may have reduced bedroom temperature in infants with eczema because of the common observation of worsening of itching in warm environments. Therefore, we also examined the final multivariable model without temperature (data not shown). Generally, ORs did not change by more than 5%, and P values did not change from significant to nonsignificant (or vice versa) at the .05 level. We kept temperature in the reported model, because it could affect other risk factors in the model even if it is not a (forward) causal variable for eczema itself.

Length at birth exhibited an inverse association to risk of eczema after confounder adjustment—that is, including adjustment for birth weight and gestational age. In contrast, gestational age and weight were previously reported to be risk factors, but length at birth was not included in these analyses.^{7,8,29} Our observation suggests an association between intrauterine growth and eczema, and lends support to the theory of intrauterine programming as a determinant of the risk of eczema.

Duration of breastfeeding was positively associated with the risk of eczema in our simple regression model ($P = .05$). The OR was essentially unchanged after confounder adjustment in the multiple regression model but dropped slightly in significance (OR, 2.80, 95% CI, 0.87-9.03; $P = .10$). Still, in our analysis, the possibility of reverse causation cannot be excluded.

Alcohol showed a positive association with the development of eczema in the simple regression model ($P = .05$), with marginal significance in the multiple regression model (OR, 1.88; 95% CI, 0.94-3.75; $P = .07$). Again, complex factors may confound such analyses and caution any general conclusion.

There was no effect on risk of eczema from surrogate markers of exposure to infections (time spent in day care and older siblings), social status, season of birth, or environmental tobacco exposure (concentration of nicotine in hair).

Conclusion

Our data suggest a strong heredity of eczema and confirm the risk associated with nonfunctional FLG allele mutations after adjustments for confounders. Remarkably few of this very comprehensive range of prenatal, perinatal, and postnatal exposures including those related to the hygiene hypothesis had any significant influence on disease expression. This risk factor profile for eczema is different from what has been reported on sensitization and asthma, emphasizing the independency of these disorders. Eczema, asthma, and sensitization are common comorbidities, but the general use of the term *atopic disease* and indiscriminate extrapolation of risk factors between these disorders may not be justified.

Perinatal exposure to dog was the only environmental exposure significantly reducing the disease manifestation, suggesting other, as yet undisclosed environmental factors driving the increasing prevalence of eczema in children. Dog exposure may be a surrogate for other exposures associated with having a dog at home such as a particular microbiology milieu or alternative lifestyle factors, which should be explored because they may hold the key to an understanding of what environmental exposure is triggering genetically susceptible individuals and is responsible for the increased disease prevalence.

The increased cumulative incidence of eczema during recent decades^{1,2} remains unexplained despite this and other comprehensive analyses of the environmental influence on disease expression.

The guarantor of the study is H.B., who has been responsible for the integrity of the work as a whole, from conception and design to conduct of the study and acquisition of data in COPSAC, analysis and interpretation of data, and writing of the article. The contributors of the study include L.B.H. and R.H., who contributed to acquisition of COPSAC data, and C.G., C.P., L.S., and M.S., who contributed to the analyses and interpretation of the data. All contributors have contributed important intellectual input and given approval of the final version of the article.

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Key messages

- There is a strong heredity in early childhood eczema, only partly explained by our recent discovery of mutation in the filaggrin gene.
- Dog exposure is associated with reduced risk of eczema and is the only environmental exposure identified of possible relevance to disease expression.

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RISK ANALYSIS OF EARLY CHILDHOOD ECZEMA

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METHODS

Cohort selection was previously described in detail.¹⁻⁶ In brief, pregnant women from greater Copenhagen with a history of physician-diagnosed asthma received mailed written information about the study (N=798), of whom 452 attended the clinic for in-depth information, and 411 accepted enrollment between August 1998 and December 2001. The cohort was comparable with the population of greater Copenhagen, except mothers of the cohort population were less likely to have given natural childbirth. The households were slightly less affluent, with fewer children and fewer pets, and white subjects may be overrepresented.¹

Statistical analyses

There are different approaches for model selection. When there is 1 key predictor variable and a few covariates, one feasible approach to test for confounding is to just look for changes in the effect estimate of the key predictor when the covariates are added/removed from the model, without regard to the *P* values. However, in our case, we have 40 predictors. Rather than test all possible combinations of variables to see how effect estimates change, a more feasible and common approach is to use stepwise selection, which is a stepwise *P* value-based method of selecting variables. Although

our main interest is not in *P* values of covariates themselves, by definition, confounders are related to both the outcome and the key predictor. Thus, variables with very high *P* values are eliminated from the list of potential confounders because they are not significantly related to the outcome. On the other hand, if a variable is significant and is added to the model, it is not necessarily a confounder, and we do not judge a variable to be a confounder if it simply has a small *P* value—that is, this process is more helpful in eliminating variables from the confounder list than in identifying confounders.

In our case, we developed a final model that included a set of variables that predict eczema by using stepwise selection. We did not build the model with a key predictor and covariates in mind, but rather considered predictors equally and determined those with at least marginal significance on the basis of an ordered stepwise selection process. However, we can still interpret this model by focusing on 1 predictor and determining the influence of other variables on that predictor by noting changes in the effect estimate from the univariable to multivariable models. Because the changes in effect estimates were generally small, the variables in the final model do not appear to be strong confounders on each other.

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TABLE E1. Total sample size and number (%) of cases for categorical variables

		No.	No. of cases (%)
Heredity			
Filaggrin mutations		352	40 (11.4)
Mother's eczema		356	172 (48.3)
Mother's allergic rhinitis		356	263 (73.9)
Father's asthma		347	42 (12.1)
Father's eczema		346	49 (14.2)
Father's allergic rhinitis		347	112 (32.3)
Demographics			
Sex: male		356	173 (48.6)
Race: white		356	346 (97.2)
Season of birth		356	Spring 73 (20.5)
			Summer 101 (28.4)
			Fall 104 (29.2)
			Winter 78 (21.9)
Social status	Mother's education	350	Elementary/Medium 218 (62.3)
			College 85 (24.3)
			University 47 (13.4)
	Mother's work	355	Unemployed 34 (9.6)
			Student 39 (11.0)
			Nonprofessional 118 (33.2)
			Professional 164 (46.2)
Pregnancy			
Previous deliveries		347	0 213 (61.4)
			1 100 (28.8)
			2 or more 34 (9.8)
3rd trimester complications	Preterm contractions	347	230 (66.3)
	Pre-eclampsia	350	19 (5.4)
	Pneumonia	356	20 (5.6)
	Influenza	356	31 (8.7)
	Asthma status	356	Worse 72 (20.2)
			Same 186 (52.3)
			Better 98 (27.5)
	Mode of delivery	356	Natural 231 (64.9)
			Cesarean section 78 (21.9)
	Vacuum		47 (13.2)
	Apgar score	351	9 or 10 338 (96.3)
3rd trimester exposures	Smoking	356	51 (14.3)
	Alcohol	356	60 (16.9)
	Antibiotics	356	49 (13.8)
	Paracetamol	356	55 (15.5)
	Physical exercise	212	None 143 (67.5)
			Once 37 (17.5)
			More than once 32 (15.1)

TABLE E2. Summary statistics for distributions of continuous variables

		No.	Percentile				
			Minimum	25th	50th	75th	Maximum
Demographics at birth							
Gestational age (wks)		356	36	39	40	41	44
Head circumference (mm)		343	305	340	350	360	390
Length (cm)		356	43	51	52	54	59
Weight (kg)		356	1.62	3.20	3.52	3.85	5.16
Social status	Family income (€1000)	355	100	380	500	600	1300
Postnatal exposures							
Diet	Duration solely breast-fed (d)*	355	0	91	131	180	534
	Duration with eggs in diet (d)*	344	0	696	760	828	953
	Duration with cow's milk in diet (d)*	354	334	791	881	913	996
	Duration with fish in diet (d)*	355	33	804	858	906	1005
Day care	Time in day care (d)*	348	0	660	748	841	955
Ambient air at age 1 y							
Environmental tobacco exposure	Nicotine in hair (ng/mg)	339	0.03	0.32	0.72	2.45	103.84
Temperature (°C)		300	15.22	19.57	20.44	21.33	24.95
Humidity (%)		300	31.81	47.35	54.42	61.82	76.62

*Up to 3 years of age.

TABLE E3. Prenatal risk factors: ORs for development of eczema by 3 years of age using heredity, demographic, and pregnancy predictors in simple logistic regression models†

		OR comparison	OR (95% CI)	P value
Heredity				
	Filaggrin mutations	Yes vs no	2.43 (1.23-4.79)	.01
	Mother's eczema	Yes vs no	3.10 (2.00-4.79)	<.0001*
	Mother's allergic rhinitis	Yes vs no	1.57 (0.97-2.57)	.07
	Father's asthma	Yes vs no	2.01 (1.04-3.87)	.04
	Father's eczema	Yes vs no	1.38 (0.75-2.52)	.30
	Father's allergic rhinitis	Yes vs no	1.83 (1.16-2.88)	.01
Demographics				
	Sex	Males vs females	1.08 (0.71-1.64)	.72
	Race	Nonwhite vs white	0.86 (0.24-3.11)	.82
	Season of birth	Summer vs fall	0.86 (0.50-1.50)	.60‡
		Winter vs fall	1.21 (0.67-2.18)	.52‡
		Spring vs fall	0.71 (0.39-1.31)	.28‡
	Gestational age	Week increase	0.94 (0.83-1.08)	.38
	Head circumference at birth	Increase (mm)	0.99 (0.98-1.01)	.37
	Length at birth	Increase (cm)	0.90 (0.82-0.99)	.03
	Weight at birth	Increase (kg)	0.71 (0.47-1.05)	.09
Social status	Family income	Increase (€10,000)	1.00 (0.99-1.01)	.68
	Mother's education	College vs Elementary/Medium	1.40 (0.85-2.32)	.19‡
		University vs Elementary/Medium	1.57 (0.83-2.96)	.16‡
	Mother's work	Student vs nonprofessional	1.13 (0.54-2.36)	.75‡
		Unemployed vs nonprofessional	2.32 (1.07-5.04)	.03‡
		Prof vs nonprofessional	1.33 (0.82-2.16)	.24‡
Pregnancy				
Previous deliveries		1 vs none	0.96 (0.59-1.54)	.85‡
		2 or more vs none	1.00 (0.48-2.07)	1.00‡
3rd trimester complications	Preterm contractions	Yes vs no	1.03 (0.66-1.62)	.89
	Pre-eclampsia	Yes vs no	1.83 (0.72-4.67)	.21
	Pneumonia	Yes vs no	0.54 (0.20-1.43)	.22
	Influenza	Yes vs no	1.43 (0.68-2.99)	.34
	Asthma status	Worse vs same	0.52 (0.30-0.93)	.03‡
		Better vs same	0.91 (0.56-1.48)	.70‡
	Mode of delivery	Cesarean section vs natural	1.08 (0.65-1.82)	.76‡
		Vacuum vs natural	0.72 (0.37-1.37)	.31‡
	Apgar score	<9 vs 9-10	1.57 (0.52-4.78)	.43
3rd trimester exposures	Smoking	Yes vs no	0.67 (0.36-1.24)	.20
	Alcohol	Yes vs no	1.74 (1.00-3.05)	.05
	Antibiotics	Yes vs no	0.65 (0.35-1.22)	.18
	Paracetamol	Yes vs no	1.30 (0.73-2.32)	.37
	Physical exercise times per week	1 vs none	1.87 (0.90-3.88)	.09‡
		>1 vs none	0.56 (0.24-1.29)	.17‡

*Significant after applying the false discovery rate procedure set at .05.

†Sample sizes available for analysis for each variable are the same as those given in Tables E1 and E2.

‡Denotes a comparison of 2 levels within a categorical variable. P values for categorical variables (as a whole): season of birth, P = .41; mother's education, P = .22; mother's work, P = .19; previous deliveries, P = .98; asthma status, P = .08; mode of delivery, P = .53; physical exercise, P = .06.

TABLE E4. Post-natal risk factors: ORs for development of eczema by 3 years of age, using postnatal exposure and ambient air by 1 year of age predictors, with simple logistic regression models†

		OR comparison	OR (95% CI)	P value
Postnatal exposures				
Cat at home at birth		Yes vs no	1.28 (0.74-2.22)	.37
Dog at home at birth		Yes vs no	0.37 (0.20-0.67)	.001*
Diet	Duration solely breast-fed (d)‡	Exposure-year increase	2.76 (1.01-7.56)	.05
	Duration with eggs in diet (d)‡	Year increase	0.94 (0.59-1.51)	.79
	Duration with cow's milk in diet (d)‡	Year increase	0.88 (0.41-1.90)	.75
	Duration with fish in diet (d)‡	Year increase	0.94 (0.43-2.03)	.87
Pillow		Use vs none	2.10 (0.22-20.48)	.40
Day care	Time in day care	Year increase	0.71 (0.46-1.11)	.13
Ambient air at age 1 y				
Environmental tobacco exposure	Nicotine in hair	1 ng/mg increase	0.95 (0.91-0.99)	.02
Temperature		1 °C increase	0.77 (0.66-0.91)	.002*
Humidity		1% increase	1.01 (0.98-1.03)	.52

*Significant after applying the false discovery rate procedure set at .05.

†Sample sizes available for analysis for each variable are the same as given in Tables E1 and E2.

‡Up to 3 years of age.