

Letter to the Editor

Infantile eczema: Prognosis and risk of asthma and rhinitis in preadolescence

To the Editor:

There is limited information on the prognosis of eczema¹ (atopic dermatitis) in infancy up to adolescence, and knowledge concerning risk factors for the development of asthma and rhinitis is scarce. Recent developments in eczema genetics and skin barrier function have highlighted the need for longitudinal studies to better understand the relationship between eczema in infancy and asthma and rhinitis later in life. We sought to examine prognoses and risk factors for eczema, asthma, and rhinitis in preadolescence among children with infantile eczema.

The Swedish population-based birth cohort BAMSE (Barn [children], Allergy, Milieu, Stockholm, Epidemiological Study) consists of 4089 children consecutively recruited from 1994 to 1996 at a mean age of 2 months.² Data on risk factors were obtained at inclusion. The current study includes 3208 children who participated at the 1-, 2-, and 12-year follow-up. The study population and the original cohort were comparable (Table I). Parental questionnaires identified children with eczema, asthma, and rhinitis on the basis of symptoms, medication, and doctors' diagnosis. A subgroup of 137 children with infantile eczema provided blood at 2 years for analyses of allergen-specific IgE. Infantile eczema was defined as dry skin, itchy rashes for 2 weeks or more with typical location (ie, face or arms/legs extension surfaces or arms/legs flexures or wrists/ankles flexures), and/or doctors' diagnosis of eczema between the ages of 3 months and 2 years.³ Definitions of health outcomes and risk factors are presented in Table E1 in this article's Online Repository at www.jacionline.org. The association between infantile eczema and allergy-related diseases in preadolescence was analyzed by using logistic regression. Risk factors that were significantly associated with eczema, asthma, or rhinitis in preadolescence in the unadjusted model were kept in the final model. Adjustment for sex and parental allergy for all analyses were decided on *a priori*. Analyses were performed with STATA Statistical Software (release 11.1; StataCorp, College Station, Tex).

Infantile eczema was present in 810 children. In preadolescence, 49.1% (95% CI, 45.7-52.6) of the children with a history of infantile eczema had an allergy-related disease and half of them had eczema. Of preadolescents with no history of infantile eczema, 22.3% (95% CI, 20.6-24.0) had an allergy-related disease (Fig 1). Children with infantile eczema had a 3-fold risk of eczema in preadolescence (adjusted odds ratio [OR], 3.97; 95% CI, 3.18-4.95) compared with children without eczema before age 2 years (see Fig E1 in this article's Online Repository at www.jacionline.org). The former group also had an increased risk of asthma (adjusted OR, 2.22; 95% CI, 1.65-2.98 [additionally adjusted for asthma before age 2 years]) and rhinitis (adjusted OR, 2.69; 95% CI, 2.22-3.26 [additionally adjusted for rhinitis before age 2 years]). To ensure that the increased risk for asthma and rhinitis in preadolescence among children with infantile eczema was not explained by preadolescents having eczema with concomitant asthma and rhinitis, we also restricted the analyses, including the 606 children with infantile eczema

TABLE I. Descriptive information of the original cohort and the final study population

	Percent (95% CI)	
	Original cohort (n = 4089)	Study population (n = 3208)
Sex (male)	50.5 (49.0-52.0)	50.7 (48.9-52.4)
Parental allergy*	43.2 (41.6-44.7)	44.5 (42.7-46.2)
Blue-collar workers	17.3 (16.1-18.5)	15.8 (14.5-17.0)
Exclusive breast-feeding ≥ 4 mo	79.5 (78.2-80.8)	80.6 (79.3-82.0)
Tobacco smoking†	24.9 (23.5-26.2)	23.9 (22.4-25.4)
Infantile eczema	25.8 (24.4-27.2)	25.2 (23.7-26.8)

*Doctor's diagnosis of asthma and/or hay fever in combination with allergy to furred pets and/or pollen and/or doctor's diagnosis of eczema at enrollment for any or both parents.

†Mother smoked at least 1 cigarette per day during pregnancy and/or any of the parents smoked at least 1 cigarette per day at the time of enrollment.

who did not have eczema in preadolescence. As a result, adjusted ORs changed to 2.06 (95% CI, 1.45-2.92) for asthma and 2.36 (95% CI, 1.89-2.96) for rhinitis.

Risk factors in infancy among children with infantile eczema for eczema, asthma, and rhinitis in preadolescence are displayed in Table II. Persistent infantile eczema was a significant risk factor for all 3 diseases and of children with a history of persistent infantile eczema, 33.3% (95% CI, 27.9-39.1) had eczema, 17.2% (95% CI, 13.0-22.1) had asthma, and 43.9% (95% CI, 38.1-49.9) had rhinitis in preadolescence (see Table E2 in this article's Online Repository at www.jacionline.org). The reference was children with infantile eczema only in their first or second year of life. We evaluated these 2 groups separately and found that among the 203 children with eczema in their first year of life, but not in their second year of life, 12.3% (95% CI, 8.1-17.6) had eczema, 10.9% (95% CI, 7.0-16.0) had asthma, and 27.2% (95% CI, 21.1-33.9) had rhinitis in preadolescence. The corresponding proportions among the 319 children with eczema in their second year of life, but not in their first year of life, were 26.3% (95% CI, 21.6-31.5), 6.94% (95% CI, 4.4-10.3), and 25.7% (95% CI, 21.0-30.9), respectively. Absolute risks for allergy-related diseases in preadolescence, for various phenotypes of infantile eczema, are presented in Table E2.

The strengths of the current study are the prospective design with yearly follow-ups during the first 2 years of life that minimize recall bias for symptoms and exposures in infancy. The large number of participants in combination with small loss to follow-up and the population-based design brings high generalizability to the results. A limitation of the study is that disease outcomes are based on questionnaire data. However, reported symptoms of eczema in infancy in our study were found to have high sensitivity (92%) and specificity (100%) in relation to clinical diagnosis by a dermatologist.⁴

Even though studies on risk factors for prognosis of eczema have been performed mainly in selected cohorts, we could confirm results from previous studies by showing that parental allergy, rhinitis before age 2 years, severity of eczema, and sensitization among children with infantile eczema were risk factors for eczema in preadolescence.⁵⁻⁸ In addition, we found

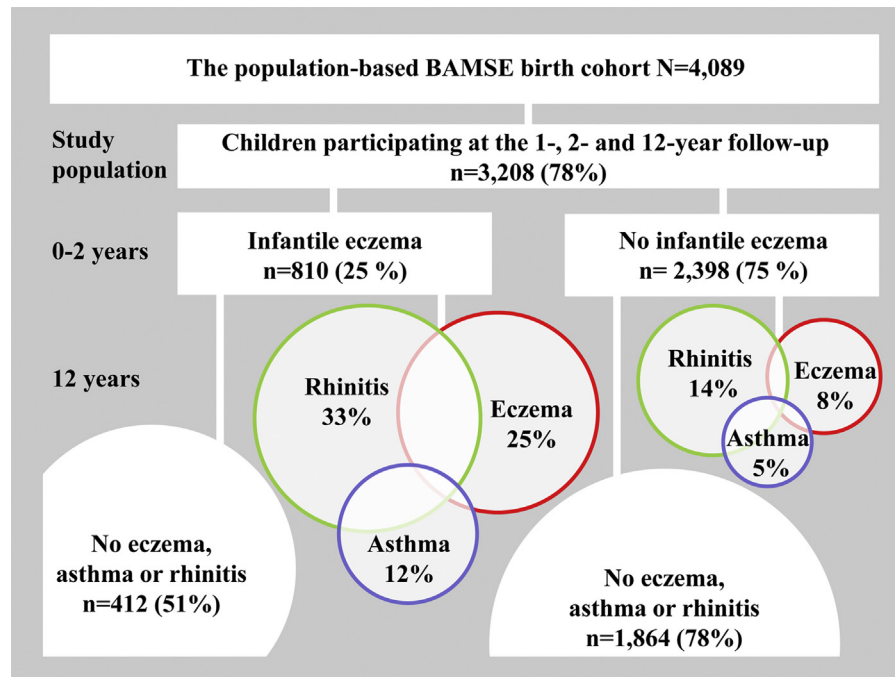


FIG 1. Subjects of the BAMSE birth cohort included in the study population and outcome of allergy-related diseases in preadolescence for children with and without infantile eczema. Venn diagrams are proportional. Because some children have more than 1 disease, the numbers add up to more than 100%.

TABLE II. Risk factors in relation to eczema, asthma, and rhinitis in preadolescence among children with infantile eczema in the BAMSE birth cohort (n = 810), adjusted analyses

Risk factors* (%) before age 2 y among children with infantile eczema	Adjusted† OR (95% CI)		
	Eczema at age 12 y (205 of 810)	Asthma at age 12 y (93 of 804)	Rhinitis at age 12 y (263 of 808)
Sex (boys vs girls) (50.9)	0.77 (0.56-1.06)	1.62 (1.03-2.53)	1.33 (0.99-1.80)
Parental allergy‡ (54.3)	1.45 (1.05-2.01)	1.96 (1.23-3.13)	1.88 (1.39-2.56)
Tobacco exposure§ (25.6)	1.42 (1.00-2.03)	1.68 (1.05-2.69)	1.03 (0.73-1.45)
Asthma before age 2 y (10.8)	1.17 (0.70-1.94)	5.83 (3.46-9.81)	1.48 (0.93-2.36)
Rhinitis before age 2 y (12.5)	1.73 (1.10-2.71)	3.15 (1.87-5.29)	2.01 (1.30-3.10)
Sleep disturbance due to itch (28.8)	1.98 (1.41-2.78)	1.84 (1.17-2.89)	1.65 (1.19-2.28)
Widespread infantile eczema (13.1)	1.60 (1.02-2.50)	1.23 (0.67-2.25)	2.46 (1.61-3.75)
Persistent infantile eczema (35.6)	1.94 (1.40-2.69)	2.05 (1.32-3.20)	2.10 (1.54-2.86)
Atopic infantile eczema (44.5)	3.10 (1.47-6.54)	3.19 (1.20-8.50)	4.32 (2.04-9.12)

Statistically significant ORs are in boldface.

*Internal missing ranged between 0% and 2%.

†Adjusted for sex and parental allergy.

‡Doctor's diagnosis of asthma and/or hay fever in combination with allergy to furred pets and/or pollen and/or doctor's diagnosis of eczema at enrollment.

§Mother smoked at least 1 cigarette per day during pregnancy and/or any of the parents smoked at least 1 cigarette per day at the time of enrollment.

||Defined as allergen-specific IgE level of 0.35 kU_A/L or more against foods and/or airborne allergens at age 2 years based on data from 137 cases.

early tobacco exposure to be a risk factor. To our knowledge, there is only 1 previous study that has explored early tobacco exposure related to prognosis of infantile eczema and no associated risk was found.⁵

Another novel finding is that children with eczema in their first year of life, but not their second year of life, have a markedly lower risk of eczema in preadolescence than do other children with infantile eczema. This is in contrast to the general view that early onset is associated with worse prognosis.⁹ Despite having half the risk of eczema in preadolescence, these children have clearly increased risks for asthma and rhinitis, which could indicate that they represent a particular phenotype. Another explanation could be that treatment of eczema, or some other

exposure in the first year of life, alters the risk of subsequent eczema but not the risk of asthma or rhinitis.

The increased risks for asthma and rhinitis among children with infantile eczema in our study remained significant even after excluding children with eczema in preadolescence, speaking in favor of an existing "atopic" march from early eczema to asthma and rhinitis.

In conclusion, almost half of the children with infantile eczema will have eczema, asthma, or rhinitis in preadolescence. Moreover, eczema in the first year of life, but not the second year of life, is associated with good prognosis of eczema but with increased risk of asthma and rhinitis in preadolescence.

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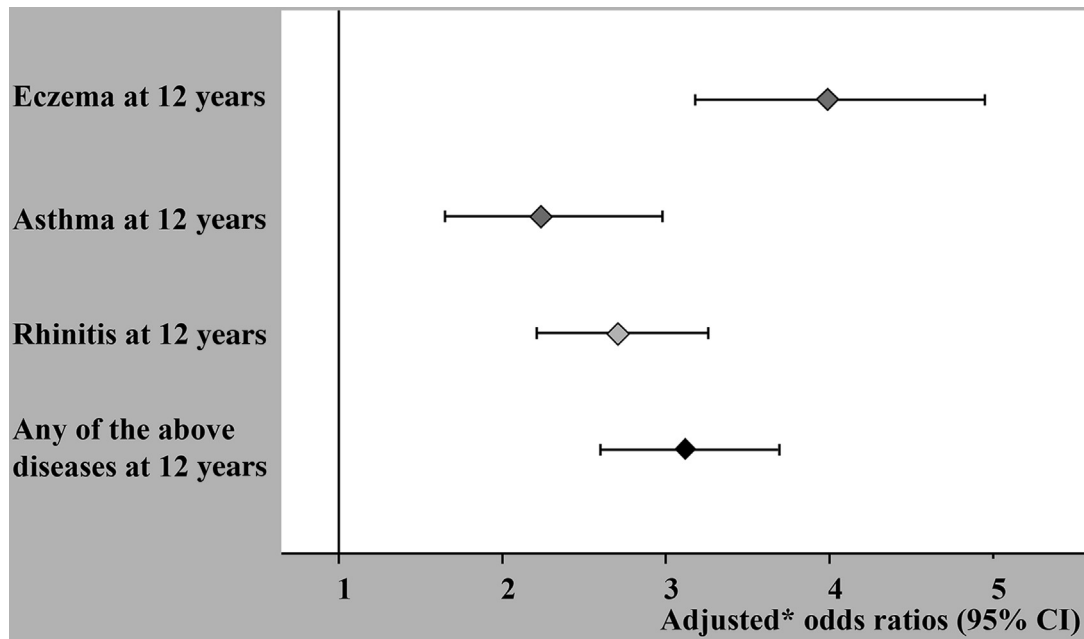


FIG E1. Increased risk for eczema, asthma, rhinitis, and any of the diseases in preadolescence, for children with infantile eczema ($n = 810$), in the population-based BAMSE birth cohort ($n = 3208$). *All ORs adjusted for sex and parental allergy. OR for asthma was additionally adjusted for asthma before age 2 years, OR for rhinitis was additionally adjusted for rhinitis before age 2 years, and OR for any disease was additionally adjusted for asthma and rhinitis before age 2 years.

TABLE E1. Definition of background variables, risk factors, and health outcomes

Variables	Definition
Background variables	
Parental allergy	Mother and/or father with doctor's diagnosis of asthma and asthma medication and/or doctor-diagnosed hay fever in combination with allergy to furred pets and/or pollen and/or doctor's diagnosis of eczema at the time of enrollment
Tobacco smoking	Mother smoked at least 1 cigarette per day during pregnancy and/or any of the parents smoked at least 1 cigarette per day at the time of enrollment
Risk factors in infancy	
Asthma before age 2 y	At least 3 episodes of wheeze between age 3 mo and 1 y, and/or between age 1 y and 2 y, in combination with inhaled steroids and/or signs of hyperreactivity without concurrent upper respiratory tract infection
Rhinitis before age 2 y	Symptoms from eyes/nose (suspected or evident) after exposure to furred pets and/or pollen and/or doctor's diagnosis of allergic rhinitis sometime between age 3 mo and 2 y
Sleep disturbance due to itch	Reported sleep disturbance due to itch, before age 2 y
Widespread infantile eczema	Defined as more than 5 body sites affected by eczema before age 1 y and/or between age 1 and 2 y. Sites (multiple-choice alternatives): face, scalp, ears, arms and/or legs, armpits, knees and/or elbows, wrist and/or ankles, hands, feet, neck, buttocks, chest and/or abdomen and/or back and/or shoulders, groin and/or genitals
Persistent infantile eczema	Having fulfilled the eczema definition in both the first and second years of life
Atopic infantile eczema	Defined as positive fx5 (allergen-specific IgE ≥ 0.35 kU _A /L) and/or positive Phadiatop (allergen-specific IgE ≥ 0.35 kU _A /L). Sera collected at age 2 y were analyzed for IgE antibodies to a mix of common inhalant allergens with Phadiatop (cat, dog, horse, birch, timothy, mugwort, <i>Dermatophagoides pteronyssinus</i> , and <i>Cladosporium herbarum</i>) and to a mix of common food allergens with fx5 (milk, egg, cod, soy, peanut, and wheat) by using the ImmunoCAP System (Thermo Fisher Scientific, Uppsala, Sweden)
Health outcomes at the 12-y follow-up	
Eczema in preadolescence	Defined as dry skin, itchy rashes with age-specific location (ie, flexures of arms/legs or wrist/ankles or neck) and/or doctor's diagnosis of eczema since the age of 10 y
Asthma in preadolescence	Defined as at least 4 episodes of wheeze in the past 12 months or at least 1 episode of wheeze in combination with occasional or regular use of prescribed inhaled glucocorticoids
Rhinitis in preadolescence	Defined as sneezing, runny or blocked nose, or itchy, red, and watery eyes after exposure to furred pets or pollen during the past 12 months, or doctor's diagnosis of allergic rhinitis since the age of 10 y

TABLE E2. Absolute risks for eczema, asthma, and rhinitis as well as for having none of the diseases in preadolescence for various combinations of risk factors up to age 2 y among children in the population-based BAMSE birth cohort (n = 3208)

Risk factors up to age 2 y (no. of children the calculations are based on)	% (95% CI)			
	Absolute risk* for eczema at 12 y	Absolute risk* for asthma at 12 y	Absolute risk* for rhinitis at 12 y	None of the diseases at 12 y
Among all children (n = 3208)				
No eczema, asthma, or rhinitis before 2 y (2086)	7.2 (6.1-8.4)	4.4 (3.6-5.4)	13.3 (11.9-14.9)	78.9 (77.1-80.7)
Among all children with infantile eczema (IE) (n = 810)				
IE (810)	25.3 (22.3-28.4)	11.6 (9.4-14.0)	32.5 (29.3-35.9)	50.7 (47.2-54.2)
IE in the first but not the second year of life (203)	12.3 (8.1-17.6)	10.9 (7.0-16.0)	27.2 (21.1-33.9)	63.9 (56.8-70.5)
IE in the second but not the first year of life (319)	26.3 (21.6-31.5)	6.94 (4.4-10.3)	25.7 (21.0-30.9)	56.0 (50.3-61.5)
Persistent IE (288)	33.3 (27.9-39.1)	17.2 (13.0-22.1)	43.9 (38.1-49.9)	35.8 (30.2-41.6)
Persistent IE causing sleep disturbance (131)	36.6 (28.4-45.5)	21.5 (14.8-29.6)	53.8 (44.9-62.6)	24.4 (17.3-32.7)
IE only, no asthma, no rhinitis (642)	24.1 (20.9-27.6)	8.0 (6.0-10.4)	30.3 (26.7-34.0)	53.4 (49.5-57.4)
IE and asthma (87)	27.6 (18.5-38.2)	36.8 (26.7-47.8)	42.5 (32.0-53.6)	42.5 (32.0-53.6)
IE and rhinitis (100)	36.0 (26.6-46.2)	27.0 (18.6-36.8)	49.5 (39.3-59.7)	31.0 (22.1-41.0)
IE and comorbidity† (152)	30.3 (23.1-38.2)	27.6 (20.7-35.5)	43.7 (35.7-52.0)	38.2 (30.4-46.4)
IE and asthma and rhinitis (35)	40.0 (23.9-57.9)	48.6 (31.4-66.0)	57.1 (39.4-73.7)	28.6 (14.6-46.3)
Among children with IE and complete data on sensitization at age 2 y (n = 137)				
IE without sensitization‡ (nonatopic IE) (76)	22.4 (13.6-33.4)	10.5 (4.7-19.7)	28.9 (19.1-40.5)	53.9 (42.1-65.5)
IE with sensitization‡ (atopic IE) (61)	45.9 (33.1-59.1)	27.9 (17.1-40.8)	65.0 (51.6-76.9)	23.0 (13.2-35.5)
Among children with IE and comorbidity† and complete data on sensitization at age 2 y (n = 26)				
IE with comorbidity,† no sensitization‡ (9)	33.3 (7.5-70.1)	33.3 (7.5-70.1)	33.3 (7.5-70.1)	22.2 (2.8-60.0)
IE with comorbidity† and sensitization‡ (17)	64.7 (38.3-85.8)	52.9 (27.8-77.0)	75.0 (47.6-92.7)	17.6 (3.8-43.4)
IE with comorbidity† and sensitization both to foods and to airborne allergens (8)	75.0 (34.9-96.8)	75.0 (34.9-96.8)	100 (59.0-100)§	0 (0-36.9)§

*Absolute risk was calculated as the number of children having both the outcome and the risk factor, divided by the total number of children with the risk factor. For 95% CIs, the binomial test of statistical significance was used.

†Comorbidity is defined as any or both of the diseases asthma and rhinitis before age 2 years.

‡Sensitization is defined as allergen-specific IgE level of 0.35 kU_A/L or more to food and/or airborne allergens.

§One-sided CI.