

Differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology

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Background: Atopic dermatitis (AD) often develops in infancy as the first manifestation of the atopic phenotype. Wheezing is also common in infancy, but it is less clear whether infant wheezing should be considered as an atopic phenotype. If infant wheeze and AD share a common aetiology, this would indicate that infant wheezing is an atopic phenotype.

Objective: To investigate whether potential risk factors for infant wheeze and AD have similar effects on these 2 phenotypes, indicating a common etiology.

Methods: A total of 34,793 mother-child pairs enrolled in the Danish National Birth Cohort were followed prospectively. Information on wheezing episodes, AD, and prenatal, perinatal, and postnatal risk factors was collected by interview at 12 and 30 weeks of gestation, at 6 and 18 months of age, and by linkage to the Danish Medical Birth Register. Data were analyzed by binary and polytomous logistic regression models.

Results: The following variables had significantly differential effects on infant wheezing and AD: parental hay fever, parental asthma, parental AD, sex, maternal age, maternal occupation, smoking during pregnancy, season of birth, birth weight, gestational age, head circumference, breast-feeding, number of older siblings, day care attendance, and pets in the home.

Conclusion: The majority of risk factors had differential effects on infant wheeze and AD indicative of a different etiology.

Infant wheezing does not seem to be etiologically linked to the epidemic of atopic disease, and infant wheezing should not be used as an indicator of the atopic phenotype. (*J Allergy Clin Immunol* 2006;117:184-9.)

Key words: Atopic dermatitis, birth cohort, epidemiology, infant, wheezing

The atopic phenotypes, such as atopic dermatitis (AD), asthma, and allergic rhinoconjunctivitis, are

Abbreviations used

AD: Atopic dermatitis
DNBC: Danish National Birth Cohort
OR: Odds ratio

epidemiologically associated and are furthermore immunologically linked by the propensity to produce IgE antibodies against common environmental allergens, a propensity also known as *atopy*. The time course for the development of atopic diseases has been described as the “atopic march.”^{1,2} AD often develops during the first year of life as the first manifestation of atopic disease, whereas asthma is often diagnosed later in childhood. In epidemiological studies, self-reported or parental-reported wheeze is the most commonly used measure of asthma prevalence.³⁻⁶ Wheezing is common in both infancy and childhood. However, although wheezing in childhood is clearly associated with atopy and atopic diseases such as AD, the relationship of wheezing in infancy to atopy and atopic diseases is less clear.^{6,7} Nonetheless, infant wheezing is often used as an indicator of an atopic phenotype.

If infant wheezing and AD represent distinct phenotypes, one would expect to find differences in the effects of potential risk factors on infant wheezing and AD. In a large prospective birth cohort, we investigated the relationship of several known risk factors to infant wheezing and AD. The aim was to elucidate whether these risk factors have differential effects on infant wheezing and AD.

METHODS

Participants

The study was based on mother-child pairs enrolled in the Danish National Birth Cohort (DNBC)⁸. Women were invited to participate when they first consulted their general practitioner about the pregnancy. Participation involved 4 computer-assisted telephone interviews at gestational weeks 12 and 30 (first and second interview) and when the child was 6 and 18 months old (third and fourth interview). The DNBC has consecutively recruited 100,000 pregnant women from 1997 to 2002. In April 2000, the fourth interview was modified and thereafter included questions about AD. The women were called as many as 4 times for each interview. If not found at home and available for interview, the interview was canceled. Almost no women actively denied participation. When the current

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study was initiated in 2002, 51,900 women were scheduled to take part in the modified fourth interview. However, 12,994 missed 1 or more of the interviews. We enrolled the 38,906 remaining pairs. Of these, a total of 4113 had missing information on 1 or more of the variables included in the analyses. Thus, 34,793 pairs were included in the current analyses. The DNBC was approved by the Ethical Committees in Denmark and by the Data Protection Board.

Definition of AD and wheezing

A diagnosis of AD was based on data obtained in the fourth interview, when the child was 18 months old. The mother was asked whether the child had ever had an itchy rash, and if so, about localization and age when affected (recorded as half-month periods). She was also asked whether the child had AD, and if so, whether a doctor had verified the diagnosis. As described elsewhere, a dermatologist examined a subgroup of the participating infants, and the combination of answers that resulted in the highest sum of sensitivity and specificity was determined.⁹ Thus, cases of AD were defined as children whose mothers reported that the child had or had had (1) an itchy rash and/or doctor-verified AD and (2) recurrent rash and/or rash for at least 4 consecutive half-months periods and (3) localization of the rash in elbow creases, behind the knees, face, wrists/hands, or generalized (4 or more localizations).

When the child was 6 months and 18 months of age, the mother was asked whether the child had ever had episodes of wheezing. If yes, age at first episode and the number of episodes were recorded. "Wheeze ever" was defined as at least 1 episode of wheezing during the period 0 to 6 months or 6 to 18 months. If the answer to the question on "wheeze ever" was yes, the mother was asked about how many episodes of wheezing the child had had since the last interview. "Recurrent wheeze" was defined as at least 3 episodes. Because the definition of AD and "recurrent wheeze" was based on repeated episodes of symptoms, subjects were only considered as cases of AD, "wheeze ever," and "recurrent wheeze" if the first episode of symptoms occurred before 15 months of age.

Definition of risk factors

Data on birth characteristics (birth weight, head circumference, and gestational age) were obtained from the Danish Medical Birth Registry. Data on other variables were obtained from the interviews. The following risk factors were considered: parental hay fever (maternal or paternal history of hay fever), parental asthma (maternal or paternal history of asthma), parental AD (maternal or paternal history of AD), sex, maternal smoking during pregnancy at 30 weeks of gestation (no, yes but not every day, every day), maternal occupation (high, medium, low, unemployed, student, other), household income (high: $\geq 500,000$ Dkr, low: $< 500,000$ Dkr, unknown), maternal age (< 25 , 25-29, 30-34, ≥ 35 years), season of birth (spring, summer, autumn, winter), birth weight (< 2500 , 2500-3000, 3000-3500, 3500-4000, ≥ 4000 g, unknown), head circumference (< 34 , 34-37, ≥ 37 , unknown), and gestational age (< 37 weeks, ≥ 37 weeks), breast-feeding (exclusive breast-feeding: ≤ 2 months, > 2 months and ≤ 4 months, > 4 months), number of older siblings (0, 1, 2, 3 or more), pets in the home (yes, no), farm residence (mother living on a farm with livestock: yes, no), and day care at 6 months of age (yes, no).

Statistical analysis

The effects of risk factors were evaluated by binary logistic regression models. The response was whether or not the child had "wheeze ever," "recurrent wheeze," or AD. The independent effects of risk factors on these three outcomes (dependent variables) were estimated by using binary logistic regression models (separate model for each dependent variable; results shown in Table I). The effects were expressed as odds ratios (ORs) with 95% CIs. The association

between "wheeze ever" and AD was examined in a logistic regression model with "wheeze ever" as the dependent variable and AD as the independent variable. This analysis was performed with and without these risk factors included as independent variables.

The comparison of the effect of a risk factor on the risk of wheeze and the effect of the same risk factor on the risk of AD was performed in a polytomous logistic regression model. In this model, 3 mutually exclusive outcomes ("wheeze ever," AD, and "wheeze ever" + AD) were compared with a unique comparison group (neither "wheeze ever" nor AD). The Wald χ^2 test of the hypothesis that the effect (OR) of a given risk factor on "wheeze ever" equals the effect of the risk factor on AD was computed (*P* values are shown in a separate column in Table I).

In a logistic regression model with "wheeze ever" (or "recurrent wheeze") as the dependent variable, it was investigated whether the effect of a given risk factor on infant wheezing was dependent on the presence of AD—that is, whether the infant had developed AD during the study. The independent variables included AD, all risk factors shown in table II, and an first-order interaction term between AD and each single risk factor. The overall *P* value for each of these interaction terms is noted in a separate column in Table II. This *P* value represents a test for whether it can be assumed that the effect of a given risk factor on the risk of wheezing is similar among infants with and without AD. Further, from this model risk estimates for the effects of risk factors on wheezing have been calculated for infants with and without AD (Table II). These analyses were also performed for "recurrent wheeze."

All data management was performed in SAS version 8.02 (SAS Inc, Cary, NC), and logistic regression analyses were performed with proc logistic and proc IML in SAS version 8.02.

RESULTS

"Wheeze ever" and AD were significantly associated (crude OR, 1.31; 95% CI, 1.21-1.42). This association remained significant after adjustment for risk factors (adjusted OR, 1.28; 95% CI, 1.19-1.39). Thus, the cumulated incidence of "wheeze ever" was 32.6% and 26.9% among infants with and without AD, respectively. The cumulated incidence of "recurrent wheeze" was 11.4% and 7.3% among infants with and without AD, respectively (adjusted OR, 1.30; 95% CI, 1.20-1.41).

The estimates for the effects of risk factors on "wheeze ever" and AD are shown in Table I. The following variables had significantly differential effects on the 2 phenotypes: parental hay fever, parental asthma, parental AD, sex, maternal age, maternal occupation, smoking during pregnancy, season of birth, birth weight, gestational age, head circumference, breast-feeding, number of older siblings, day care attendance, and pets in the home. Only 2 risk factors (farm residence and household income) did not have significantly differential effects on "wheeze ever" and AD. The effects of paternal history of asthma, hay fever, and AD on "wheeze ever" and AD were reasonably similar to the corresponding effects of maternal history of asthma, hay fever, and AD, respectively (data not shown). The results for "recurrent wheeze" were essentially similar to those for "wheeze ever" (data not shown). The risk estimates for the effects of risk factors obtained by polytomous logistic regression were essentially similar to those obtained by binary logistic regression and presented in Table I.

TABLE I. The relationship of different risk factors to the incidence of wheeze ("wheeze ever") and AD during the first 18 months of life in a Danish birth cohort (n = 34,793)

Risk factors		Incidence of "wheeze ever"		Incidence of AD		P value for similar effect†
		n (%)	OR*	n (%)	OR*	
Exclusive breast-feeding	≤2 mo	1859 (32.5%)	1	473 (8.3%)	1	<.001
	≤4 mo	3727 (28.4%)	0.87 (0.81, 0.93)	1279 (9.7%)	1.14 (1.02, 1.27)	
	>4 mo	3974 (24.9%)	0.76 (0.71, 0.81)	1575 (9.9%)	1.12 (1.00, 1.25)	
Sex	Boy	5597 (31.6%)	1	1874 (10.6%)	1	.001
	Girl	3963 (23.2%)	0.65 (0.62, 0.68)	1453 (8.5%)	0.79 (0.73, 0.85)	
Parental asthma	No	7639 (26.1%)	1	2628 (9.0%)	1	<.001
	Yes	1921 (34.8%)	1.42 (1.33, 1.52)	699 (12.7%)	1.09 (0.99, 1.20)	
Parental AD	No	7920 (27.0%)	1	2183 (7.4%)	1	<.001
	Yes	1640 (30.2%)	1.09 (1.02, 1.16)	1144 (21.1%)	3.15 (2.90, 3.42)	
Parental hay fever	No	5040 (26.2%)	1	1540 (8.0%)	1	.036
	Yes	4520 (29.0%)	1.10 (1.05, 1.16)	1787 (11.5%)	1.22 (1.13, 1.32)	
Season of birth	Autumn	2118 (29.1%)	1	805 (11.1%)	1	<.001
	Winter	2221 (27.0%)	0.89 (0.83, 0.96)	897 (10.9%)	1.01 (0.91, 1.12)	
	Spring	2945 (26.3%)	0.84 (0.79, 0.90)	964 (8.6%)	0.76 (0.68, 0.84)	
	Summer	2276 (28.2%)	0.94 (0.88, 1.01)	661 (8.2%)	0.72 (0.64, 0.80)	
Gestational age	≥37 wk	9117 (27.2%)	1	3239 (9.7%)	1	.003
	<37 wk	443 (33.4%)	1.18 (1.03, 1.35)	88 (6.6%)	0.78 (0.61, 1.00)	
Head circumference	<34 cm	1341 (28.2%)	1.02 (0.94, 1.10)	369 (7.8%)	0.86 (0.76, 0.98)	.001
	34-37 cm	5822 (26.6%)	1	2143 (9.8%)	1	
Birth weight	≥37 cm	2397 (29.5%)	1.12 (1.05, 1.19)	815 (10.0%)	0.94 (0.86, 1.04)	.008
	<2500 g	291 (36.6%)	1.43 (1.20, 1.72)	43 (5.4%)	0.72 (0.51, 1.02)	
	2500-3000 g	815 (28.2%)	1.03 (0.93, 1.13)	255 (8.8%)	1.05 (0.90, 1.22)	
	3000-3500 g	2707 (27.0%)	1	914 (9.1%)	1	
	3500-4000 g	3432 (27.0%)	0.96 (0.91, 1.03)	1232 (9.7%)	1.03 (0.93, 1.13)	
	≥4000 g	2315 (27.7%)	0.93 (0.86, 1.00)	883 (10.6%)	1.12 (1.00, 1.25)	
Farm residence	No	8894 (27.6%)	1	3121 (9.7%)	1	.350
	Yes	666 (26.4%)	0.96 (0.87, 1.06)	206 (8.2%)	0.91 (0.78, 1.07)	
Maternal age	<25 y	905 (32.5%)	1	203 (7.3%)	1	<.001
	25-29 y	3750 (27.8%)	0.82 (0.75, 0.90)	1274 (9.4%)	1.29 (1.10, 1.52)	
	30-34 y	3543 (27.0%)	0.74 (0.67, 0.82)	1360 (10.4%)	1.51 (1.28, 1.79)	
	≥35 y	1362 (25.2%)	0.65 (0.58, 0.73)	490 (9.1%)	1.37 (1.13, 1.66)	
Maternal occupation	Low	3749 (29.6%)	1	1056 (8.3%)	1	<.001
	Med	2256 (27.2%)	1.01 (0.94, 1.07)	866 (10.4%)	1.14 (1.04, 1.26)	
	High	1010 (25.1%)	0.93 (0.86, 1.02)	423 (10.5%)	1.10 (0.97, 1.24)	
	Other	835 (23.5%)	0.80 (0.73, 0.87)	351 (9.9%)	1.09 (0.96, 1.25)	
	No job	821 (28.6%)	0.90 (0.82, 0.99)	273 (9.5%)	1.12 (0.97, 1.30)	
	Student	889 (26.2%)	0.89 (0.81, 0.97)	358 (10.5%)	1.19 (1.05, 1.36)	
Household income	Low	3823 (28.7%)	1	1213 (9.1%)	1	.847
	High	4544 (26.6%)	0.97 (0.92, 1.03)	1720 (10.1%)	1.03 (0.95, 1.12)	
	Unknown	1193 (27.1%)	0.95 (0.88, 1.03)	394 (9.0%)	1.00 (0.88, 1.13)	
Number of older siblings	0	3799 (24.5%)	1	1464 (9.5%)	1	<.001
	1	4127 (30.9%)	1.52 (1.44, 1.61)	1324 (9.9%)	1.01 (0.93, 1.10)	
	2	1322 (27.0%)	1.36 (1.26, 1.48)	444 (9.1%)	0.91 (0.80, 1.03)	
	≥3	312 (29.1%)	1.57 (1.35, 1.82)	95 (8.9%)	0.90 (0.72, 1.14)	
Day care at 6 months of age	No	7978 (26.3%)	1	2948 (9.7%)	1	<.001
	Yes	1582 (35.7%)	1.48 (1.38, 1.59)	379 (8.5%)	0.96 (0.86, 1.08)	
Pets in the home	No	5493 (27.3%)	1	2122 (10.5%)	1	.021
	Yes	4067 (27.8%)	0.96 (0.92, 1.01)	1205 (8.2%)	0.85 (0.79, 0.92)	
Smoking during pregnancy	No	7529 (25.9%)	1	2868 (9.9%)	1	<.001
	Less than every day	155 (30.5%)	1.22 (1.01, 1.49)	52 (10.2%)	1.07 (0.80, 1.44)	
	Every day	1876 (35.7%)	1.46 (1.36, 1.56)	407 (7.7%)	0.87 (0.78, 0.98)	

*Risk estimates (ORs with 95% CIs) for the effects of risk factors have been obtained for each dependent variable in a separate binary logistic regression model adjusted for variables shown in the table.

†P value represents the test for equal estimates of the effect of each risk factor on the 2 dependent variables ("wheeze ever" and AD) obtained from a polytomous logistic regression model.

TABLE II. Effect of risk factors on the risk of “wheeze ever” among infants with and without AD (infants who had developed AD or not during the first 18 months of life)

Risk factors		Risk of “wheeze ever”*		P value for interaction†
		Infants without AD (n = 31,466)	Infants with AD (n = 3327)	
Exclusive Breast-feeding	≤2 mo	1	1	.599
	≤4 mo	0.87 (0.81, 0.94)	0.86 (0.69, 1.08)	
	>4 mo	0.76 (0.71, 0.82)	0.70 (0.55, 0.87)	
Sex	Boy	1	1	.006
	Girl	0.64 (0.61, 0.67)	0.81 (0.69, 0.94)	
Parental asthma	No	1	1	.745
	Yes	1.42 (1.32, 1.52)	1.47 (1.21, 1.77)	
Parental AD	No	1	1	.468
	Yes	1.04 (0.96, 1.12)	1.11 (0.94, 1.30)	
Parental hay fever	No	1	1	.972
	Yes	1.10 (1.04, 1.16)	1.09 (0.93, 1.28)	
Season of birth	Autumn	1	1	.683
	Winter	0.89 (0.82, 0.96)	0.90 (0.73, 1.10)	
	Spring	0.85 (0.79, 0.91)	0.85 (0.69, 1.04)	
	Summer	0.94 (0.87, 1.01)	1.06 (0.85, 1.33)	
Gestational age	≥37 wk	1	1	.245
	<37 wk	1.16 (1.00, 1.34)	1.57 (0.96, 2.56)	
Head circumference	<34 cm	1.02 (0.94, 1.11)	1.02 (0.78, 1.33)	.349
	34-37 cm	1	1	
	≥37 cm	1.10 (1.03, 1.18)	1.28 (1.05, 1.56)	
Birth weight	<2500 g	1.45 (1.21, 1.75)	1.28 (0.63, 2.59)	.340
	2500-3000 g	1.01 (0.91, 1.12)	1.11 (0.80, 1.53)	
	3000-3500 g	1	1	
	3500-4000 g	0.94 (0.88, 1.01)	1.16 (0.96, 1.41)	
	≥4000 g	0.91 (0.84, 0.99)	1.09 (0.87, 1.38)	
Farm residence	No	1	1	.135
	Yes	0.94 (0.85, 1.04)	1.21 (0.89, 1.65)	
Maternal age	<25 y	1	1	.057
	25-29 y	0.84 (0.76, 0.92)	0.62 (0.45, 0.85)	
	30-34 y	0.76 (0.69, 0.85)	0.48 (0.34, 0.67)	
	≥35 y	0.67 (0.60, 0.76)	0.43 (0.29, 0.63)	
Maternal occupation	Low	1	1	.696
	Med	1.01 (0.94, 1.08)	0.98 (0.80, 1.19)	
	High	0.93 (0.85, 1.02)	0.98 (0.76, 1.28)	
	Other	0.79 (0.72, 0.86)	0.93 (0.71, 1.22)	
	No job	0.89 (0.81, 0.98)	1.01 (0.76, 1.35)	
	Student	0.89 (0.81, 0.98)	0.84 (0.64, 1.10)	
Household income	Low	1	1	.233
	High	0.96 (0.90, 1.01)	1.12 (0.94, 1.32)	
	Unknown	0.95 (0.87, 1.03)	1.00 (0.77, 1.28)	
Number of older siblings	0	1	1	.028
	1	1.53 (1.44, 1.63)	1.48 (1.24, 1.76)	
	2	1.33 (1.22, 1.45)	1.78 (1.38, 2.30)	
	≥3	1.51 (1.29, 1.77)	2.29 (1.45, 3.61)	
Day care at 6 months of age	No	1	1	.518
	Yes	1.49 (1.39, 1.60)	1.38 (1.10, 1.73)	
Pets in the home	No	1	1	.945
	Yes	0.97 (0.92, 1.02)	0.96 (0.82, 1.13)	
Smoking during pregnancy	No	1	1	.688
	Less than every day	1.22 (0.99, 1.50)	1.25 (0.69, 2.26)	
	Every day	1.45 (1.35, 1.55)	1.61 (1.28, 2.01)	

*ORs (95% CIs) obtained in a logistic regression model with “wheeze ever” as the dependent variable and all variables shown in the table including AD and interaction terms between AD and each single risk factor.

†P value for test for interaction between each risk factor and AD.

It was further investigated whether the effect of risk factors on the risk of wheeze was dependent on the presence of AD—that is, whether the infant developed AD during the study period. It appears that only the effects of sex ($P = .006$) and number of older siblings ($P = .028$) were significantly dependent on the presence of AD (Table II). However, the direction of the effects of these 2 risk factors was the same no matter whether the child had developed AD or not (Table II). For “recurrent wheeze,” none of the effects of risk factors were significantly dependent on the presence of AD (data not shown).

DISCUSSION

We found that the majority of risk factors had differential effects on the risk of wheezing and AD. Most risk factors even had opposite direction of their effects on wheeze and AD. For example, breast-feeding was associated with a decreased risk of wheezing but an increased risk of AD. Hence, these findings support the notion that infant wheezing and AD have a different etiology.

The association between infant wheeze and AD observed in the current study was relatively weak (OR, 1.3). However, this appears to be consistent with other birth cohort studies. In Germany, Illi et al¹ found a similar weak association between manifestations of AD during the first 2 years of life and early wheeze (any wheeze during the first 3 years of life)—that is, the frequency of early wheeze was 41% and 32% among infants with and without AD. In the Tucson Children's Respiratory Study, it was found that eczema during the first year of life was not significantly associated with “transient early wheezing” (OR, 1.3; 95% CI, 0.7-2.5), but was significantly associated with “persistent wheezing” (OR, 2.4; 95% CI, 1.3-4.6).¹⁰ In the same study it was demonstrated that “transient early wheezing” was not related to total IgE and skin prick test reactivity against inhalant allergens at 6 years of age, whereas this was the case for the “persistent” phenotype. This suggests that “early transient wheezing” is not related to atopic conditions such as atopy, eczema, or rhinitis. In the current study, the length of follow-up does not allow us to determine whether infant wheezing and AD are associated with persistent wheezing or asthma in childhood.

The mother of a child having had wheeze (or AD) may be more aware of other symptoms, such as from the skin (or respiratory tract), resulting in information bias. Moreover, the probability of 1 disease being diagnosed by a physician may depend on the presence of another, resulting in Berkson bias.¹¹ These biases may tend to produce false-positive associations between truly unrelated diseases. It is conceivable that the observed weak positive association between wheeze and AD could at least partly be a result of these potential biases. Many birth cohort studies have been conducted in high-risk infants, and studies in such selected populations may be more prone to produce biased associations. The current design was a prospective population-based birth cohort study, which

may be less prone to produce biased estimates of exposure-disease associations.

With the exception of sex and number of older siblings, the effects of risk factors on infant wheeze were not dependent on whether the infant had developed AD (Table II). Thus, the etiology of infant wheeze does not appear to differ between infants with AD (“atopic wheeze”) and without AD (“nonatopic wheeze”), lending little support to the hypothesis of a distinct atopic wheezing phenotype in infancy.

Day care attendance, older siblings, and lack of breast-feeding were positively associated with infant wheezing, but tended to be negatively associated with AD. These findings are consistent with the notion that these risk factors increase the risk of infections, which in turn increases the risk of infant wheezing illness. Conversely, microbial exposure has been hypothesized to be protective against atopic diseases such as AD, hay fever, and allergic asthma. Accordingly, in a retrospective study, Rusconi et al¹² found that day care attendance, siblings, and lack of breast-feeding were positively associated with transient early (first 2 years) wheezing. In contrast, in the same study, these factors were negatively associated with late-onset wheezing, a wheezing phenotype that was more clearly associated with eczema and allergic rhinitis at 6 years of age.

Consistent with previous studies, smoking during pregnancy was a significant risk factor for infant wheezing.^{13,14} This association may be a result of the fact that smoking during pregnancy decreases postnatal lung function¹⁵ and possibly also increases the susceptibility to infections. In contrast, smoking during pregnancy has been associated with a decreased risk of atopy (IgE sensitization) and eczema in the offspring,^{16,17} which is in line with the current data.

In conclusion, the majority of risk factors examined had differential effects on infant wheeze and AD, emphasizing that these phenotypes have a different etiology. Changes in the prevalence of these risk factors are likely to have differential effects on trends in the prevalence of infant wheezing and atopic diseases. The observed weak association between wheeze and AD should be seen in the light of potential biases tending to overestimate the association between diseases. Thus, our data suggest that infant wheeze is not etiologically linked to the epidemic of atopic disease and that infant wheeze should not be used as an indicator of the atopic phenotype.

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Correction

With regard to the November 2005 article entitled “*In vivo* assessment with prick-to-prick testing and double-blind, placebo-controlled food challenge of allergenicity of apple cultivars” (2005;116:1080-6): The following text should have appeared as a footnote in the disclosure information of this article:

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