

Early life factors related to clinical manifestations of atopic disease but not to skin-prick test positivity in young children

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The relative influence of early life events in the development of IgE-mediated allergy is still undetermined. We investigated early life factors in relation to skin-prick test (SPT) positivity and clinical manifestations of atopic disease in a population-based sample of 201 Italian children (3 months–5 years), after considering their interactions with known determinants of allergy. Among them, 143 children had SPT performed to common allergens. Threatened abortions, general anesthesia at delivery, prematurity, birthweight < 2500 g, maternal smoking, dampness and gas heating exposure were all significantly related to an increased risk of frequent rhinitis in the absence of cold (18%). *In utero* smoking, threatened abortions, fetal health complications, infantile colic, maternal smoking in childhood (satisfactorily correlated with maternal expired CO during the survey) and respiratory infections were all independent determinants of frequent wheezing (23%). Doctor's diagnosis of asthma (3%) was related to *in utero* smoking, being born in spring, infantile colic and respiratory infections. A simultaneous exposure to *in utero* smoking and infantile colic put the infants to a fourfold higher risk of frequent wheezing and to a ninefold risk of asthma, respectively. Having a pet and washing blankets at <60°C were inversely related to frequent wheezing. Data confirmed also that maternal phenotype influences the inheritance of atopic disease. No event, except a low intake of fruit (<3/week), was significantly associated with positive SPT (20%) or eczema. Besides allergic sensitization, other events, which occur early in life, seem critical to the development of IgE-mediated allergy.

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The incidence of IgE-associated conditions such as asthma, allergic rhinitis and atopic dermatitis has increased considerably over the past decades in industrialized countries. The fact that genetic stock has not changed over this time, points to an increase in host susceptibility due to unknown factors and/or to the intervention of a more toxic environment (1).

Studies, which have investigated the link between the increase of allergy and environmental changes, such as in pollution levels (2), have not been conclusive and further risk factors for the development of allergy require investigation.

Recent data support the hypothesis that determinants for atopic diseases may be crucial

already in early life when the infant's immune system hovers in the balance between the Th1 and the Th2 type of response to exogenous exposure (3). However, data are scanty. Antenatal and postnatal exposures to allergens (4), head circumference at birth (5,6) and pregnancy outcomes (6,7) have also been related to the development of allergic sensitization and atopic disease. Hence, more detailed information on early life is needed either to understand the mechanisms, which underlie the development of atopic disease, or to explain new trends in its prevalence.

In industrialized countries, infertility has been largely overcome, pregnancies more often proceed to term, and the proportion of stillbirths as well as

the infant mortality rate have steadily declined over the past few decades. It cannot be excluded that the increase in host susceptibility at an organ level, which has been evoked to explain the augmentation of atopic disease prevalence (1), results from the observed substantial improvement in pregnancy outcome.

We investigated early life factors in relation to skin-prick test (SPT) positivity to common allergens and clinical manifestations of atopic disease including the symptoms by which this usually starts in early childhood, using data from a population-based sample of children. Particular attention was given to the role of antenatal and perinatal factors, on which there is scanty evidence, and to eventual interactions they have with other known risk factors for respiratory and atopic diseases, namely male gender, familial history of allergy and parental smoking.

Methods

This survey was carried out from September 1993 to November 1994 among 201 children, aged between 3 months and 5 years, who were recruited in three vaccination centres of a rural zone of southern Italy (Basilicata), where response rate to vaccination has been reported to be high (95%). In one center after the other, the entire sample of the children having to be vaccinated during 5–6 months was recruited to participate in the survey. According to the vaccination schedule, children were aged 3, 5, 11 months, 2.5 and 5–6 years, respectively. Children who did not attend the vaccination centers were traced and seen at home. The physician interviewed each child's mother using a structured interview and a standardized questionnaire. There were no refusals to the interview. The field survey was entirely conducted by the same trained physician (GM).

Health outcomes

Skin-prick test positivity. Owing to the young age of children, SPT were performed with an ISITEST® Multi-Test device (SARN, Rome, Italy), which has been shown to be reproducible and to reduce the risk of false-positive results (8), using standardized allergenic extracts (Dome-Hollister-Stier-Bayropharm, Milan, Italy). This device consists of a sterile, disposable, self-loading applicator, which applies uniform amounts of allergens at eight evenly spaced test sites. Six allergens were used: *Dermatophagoides Pteronissinus*, cat dander, *Lolium* (rye grass), *Parietaria* (wall pellitory), *Alternaria tenuis*, β -

lactoglobulin (milk) as well as a negative and a positive (histamine hydrochloride) control. Reactions were measured 15 min after the pricks. The contours of each wheal were outlined with a fine felt-tip pen and then transferred to a record sheet by means of translucent tape. The largest and the orthogonal diameter of each wheal were measured and the arithmetic mean was calculated. In agreement with previous studies, positivity was defined as a mean wheal diameter of at least 3 mm to at least one of the allergens and greater than the negative control. Informed consent to perform SPT was obtained from parents. The physician was trained with such a device before starting the survey. Reproducibility was tested as follows: three series of skin-prick tests were performed on 10 allergic volunteers aged between 3 months and 5 years. As a result, a coefficient of variation (CV) (standard deviation as a percent of the mean) of 19% was obtained, which is considered as good according to the International Study of Asthma and Allergy in Childhood (ISAAC) criteria ($CV \leq 20\%$). Because of technical problems or refusals, SPT data were available only for 143 out of 201 children (70%).

Clinical manifestations of atopic disease. The following two types of outcomes were considered:

- atopic diseases diagnosed by a doctor, namely allergic rhinitis [not considered in the analysis because it was much too rare (1.5%)], asthma and eczema;
- symptoms by which atopic diseases frequently start in early childhood, such as rhinitis (has your child ever had frequent sneezy, stuffy or runny nose apart from cold?), frequent wheezing (frequent wheezing or whistling in the chest?) and frequent dry cough at night (frequent dry cough at night, apart from a cough associated with cold?).

Risk factors

Antenatal and perinatal. In spite of the fact that maternal recall has been considered as fully satisfactory in the case of pregnancy outcomes and child's early life (9), data on child's early life and pregnancy from which the child was born were obtained through a structured interview validated using mother's personal medical records (prescriptions, medical examinations and tests...) or the child's 'health carnet'. Clinical information concerned hormone intake during pregnancy, threatened abortion during pregnancy, caesarean section, general anesthesia at delivery, as well as mother's occupation during pregnancy. Additional child's early life factors encompassed health complications of the fetus during pregnancy that required medical supervision (fetal

distress, amniotic liquid deficit, placenta previa), prematurity (<37 weeks), birthweight < 2.500 g, season of birth, malformations, dyspnoea at birth, hospital admission at birth due to child's illness or health complication, breast feeding and frequent infantile colic.

Environmental. Exposures during early life assessed through a standardized questionnaire comprised parental smoking, dampness (either living in a humid zone or having dampness in the bedroom), vehicular traffic exposure, pets (cat, dog, bird etc.), washing blankets at less than 60°C, type of heating (non-centralized, gas or coal, respectively), frequent fruit intake as an indirect marker of a diet rich in vitamin C (low intake $\leq$ 3 times a week), and day nursery attendance. Particular attention was given to parental tobacco smoking for which we had both a subjective and an objective measure. The former measure, by parental reporting according to the questionnaire, included smoking habit during pregnancy for the mother and smoking habits after pregnancy for both parents; the latter measure consisted of an objective assessment of the expired carbon monoxide (CO) of both parents at the period of the survey, using a Smokerlyzer Micro® (Bedfont, Sittingbourne, England, UK), which measures expired CO (p.p.m) by generating a current proportional to CO concentration in the airways. Expired CO is known to be highly correlated with blood COHb that is a marker of smoke exposure. Unfortunately, only 41 fathers accompanied their wife and could perform expired CO assessment.

Individual and socio-economic. Respiratory infections assessed through the questionnaire included bronchitis, pneumonia or bronchiolitis during the first 6 months or the first 2 years of life as well as hospital admission for respiratory disease in early childhood. Respiratory infections did not include wheezy bronchitis, which was recorded separately. Parental education level and history of atopic diseases were also recorded.

Questions on health and risk factors were derived from the standardized questionnaires of the American Thoracic Society, the International Study of Asthma and Allergies in Childhood, and the Italian Study on Respiratory Problems in Childhood and the Environment (SIDRIA) (the Italian equivalent of ISAAC).

Statistical analysis

Differences in proportions were evaluated using the χ^2 test. Correlation analysis was used to examine the relationship between the assessment of expired CO and the number of cigarettes smoked. Initially, relations of risk factors to

health outcomes were estimated by a multiple stepwise logistic regression in which age and sex were included and presented as adjusted odds ratios (ORs) (10). Successively, the various risk factors simultaneously were included in the logistic model in order to take potential confounding into account. Furthermore, the OR for the joint exposure to two risk factors, in the case of *in utero* smoking (A) and infantile colic (B), was introduced. Under the non-interaction assumption, if the two risk factors A and B each have additive effects on prevalence, calculation shows that the combined risk is estimated by $ORA + ORB - 1$ obtained by contingency tables (11). As there are few or no data on the influence of early life risk factors in the development of atopic disease, the study was intended from the beginning to be a hypothesis generator and not to test statistical hypotheses so that a p-value <0.05 was considered as sufficient to establish statistical significance. All the analyses were performed with the BMDP software.

Results

Characteristics of the sample

Data on health outcome and risk factors were available for 201 infants except for SPT positivity, which could be assessed only in 143 infants. Children not having SPT performed differed only in age from those who had it performed. As expected, they were younger (47% among $\leq$ 1 year vs. 28% >1 year; $p < 0.01$). One hundred and six children were boys. Sixteen percent were aged <1 year, 27.9% between 1 and 2 years, 19.9% between 2 and 3 years, 19.4% between 3 and 4 years and 16.9% >4 years. Mean and median age were 23.5 months (SD=12.3 months) and 21.4 months, respectively. Ninety-seven percent had never moved from their villages. No day nursery existed in the considered zones.

Distribution of clinical manifestations of atopic disease and SPT positivity

Besides SPT positivity, which was present in 20%, eczema was the most frequent atopic disease in both sexes (Table 1). Wheezing was the most common symptom followed by rhinitis and dry cough at night. In this region of Italy, rye grass was the most common sensitizing allergen, followed by *Alternaria*. No clear effect of sex and age on health outcome prevalence was observed except in the case of SPT positivity, which increased significantly ($p < 0.05$) with age and was globally more frequent ($p < 0.05$) among

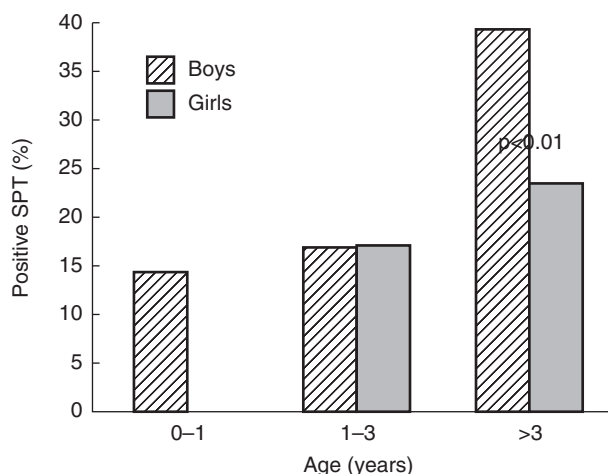


Fig. 1. Percentage prevalence of skin-prick test (SPT) positivity according to sex and age (n=143).

boys (Figs 1 and 2), except in the case of cat dander and *D. Pteronissinus*.

Relationships to early life risk factors

No significant relationship existed of early life events to SPT positivity or eczema, except in the case of low fruit intake (frequency 31.3%) (OR=3.7, 95% confidence interval 1.1–12.5 and OR=2.7, 95%CI 1.1–6.8, respectively). On the contrary, clinical manifestations of atopic disease such as frequent rhinitis, frequent wheezing and asthma, but not frequent dry cough at night, were significantly related to various early life risk factors as summarized in Fig. 3.

Antenatal and perinatal

Frequent rhinitis was significantly associated with threatened abortion during the second and third trimester of pregnancy (8.4%) (OR=3.7, 95%CI 1.3–10.4), general anesthesia at delivery (38.6%) (OR=1.8, 95%CI 1.1–3.3), prematurity (7.9%) (OR=10.7, 95%CI 2.8–39.9), or birthweight <2500 g (5.9%) (OR=4.1, 95%CI 1.2–14.4). Frequent wheezing was significantly linked with threatened abortion at any time during pregnancy (16.3%) (OR=4.5, 95%CI 1.6–12.4), health complications of the fetus (4.0%) (OR=6.6, 95%CI 1.5–29.8), *in utero* smoking (12.2%) (OR=3.2, 95%CI 1.3–8.2) or infantile colic (15.8%) (OR=3.3, 95%CI 1.5–7.4). Diagnosed asthma was associated with having been exposed to smoking *in utero* (3.3 95%CI 1.0–10.6), being born during spring (31.2%) (OR=1.8; 95%CI 1.2–20.6) or having had infantile colic (OR=6.6, 95%CI 1.2–35.9).

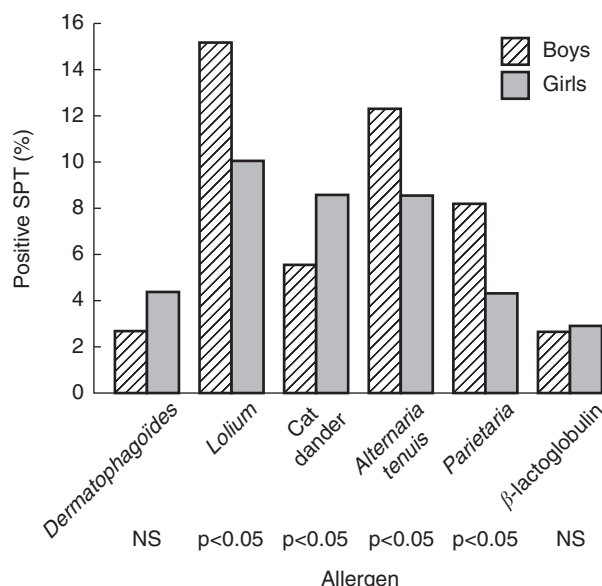


Fig. 2. Percentage prevalence of skin-prick test (SPT) positivity to common allergens according to sex (n=143).

Individual and socio-economic

Respiratory infections in the first 6 months of life (10.9%) were strongly associated with both frequent wheezing (OR=4.8, 95%CI 1.9–12.2) and diagnosed asthma (OR=24.6, 95%CI 3.8–157.0). Maternal history of asthma was more frequently reported in children with diagnosed asthma (OR=7.7, 95%CI 1.2–47.5) than in others. This association was even stronger if only boys were considered in the analysis. No significant relationship existed with paternal asthma. Only a trend existed between parental history of allergy (17.2% maternal and 8.1% paternal, respectively) and atopic symptoms in this sample. No effect of education was seen, but a higher father's education (6.0% university vs. 30.5% high school and 63.5% others, respectively) was strongly related to eczema (OR=7.2, 95%CI 1.0–52.3).

Table 1. Percentage prevalence (%) of clinical manifestations of atopic disease according to age and sex among Italian children (n=201)

Symptoms	All	Boys		Girls	
		≤1 year (n=29)	>1 year (n=77)	≤1 year (n=18)	>1 year (n=77)
Frequent sneezy nose	18.3	24.1	20.8	27.8	11.7
Frequent runny nose	9.9	6.9	10.4	0.0	13.0
Frequent stuffy nose	17.8	24.1	18.2	11.1	16.9
Wheezing	22.9	27.6	19.5	27.8	23.7
Night cough	9.2	0.0	6.7	5.6	16.0
Asthma	3.0	0.0	3.9	0.0	4.1
Eczema	8.0	0.0	13.0	0.0	7.8
Skin-prick test positivity	20.3	12.5	24.6	0.0	18.7

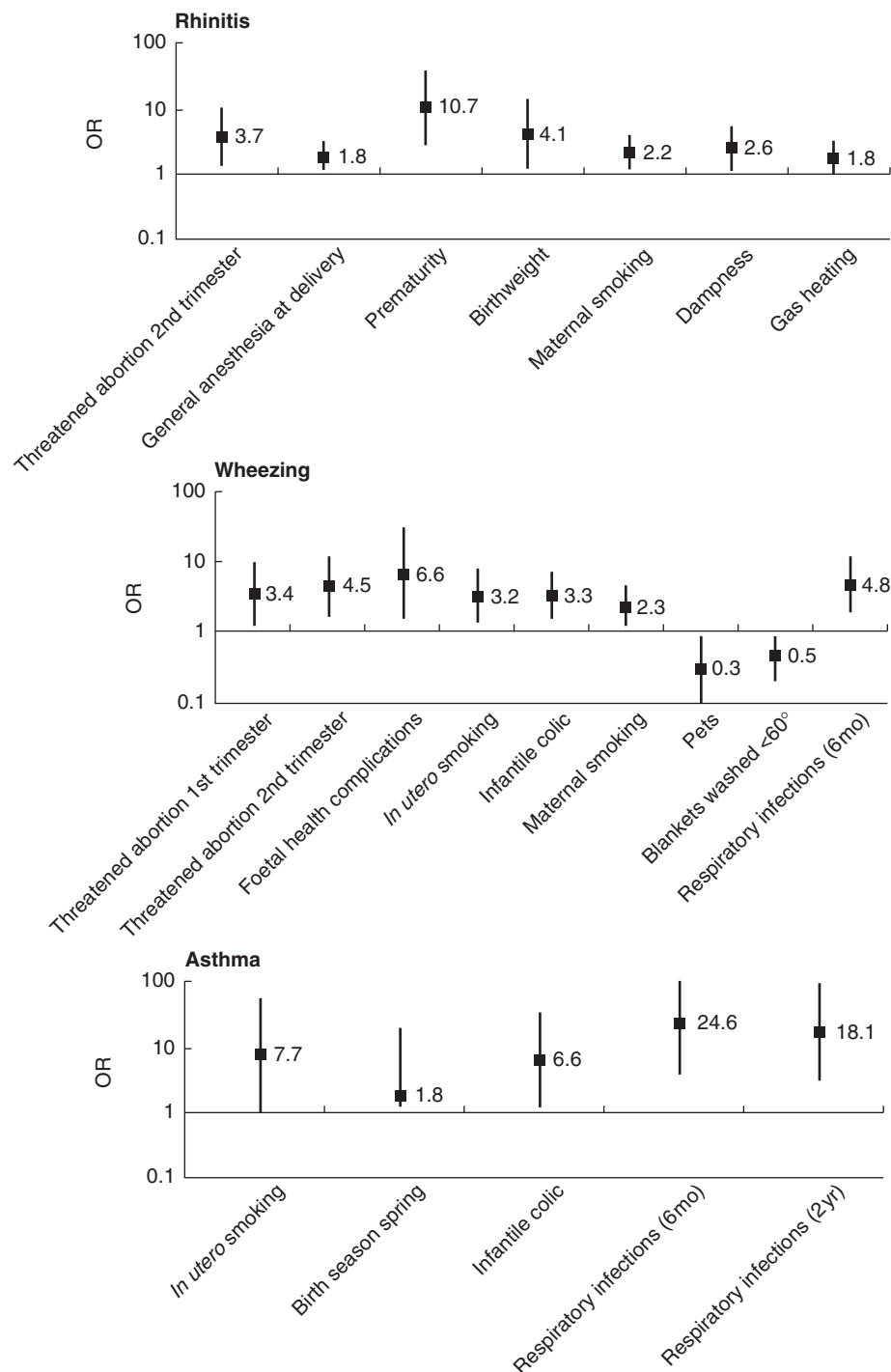


Fig. 3. Sex and age-adjusted odd ratio for early life risk factors related to frequent rhinitis, frequent wheezing and asthma. Vertical lines represent a 95% confidence interval.

Environmental

Maternal smoking (35.8%) in early life was significantly related to frequent rhinitis (OR=2.2, 95%CI 1.2–4.1) and frequent wheezing (OR=2.3, 95%CI 1.2–4.7) whereas paternal smoking (69.8%) was not. Mothers of children with frequent wheezing smoked 25 cigarettes on average during the period of the survey. Results

between maternal smoking and frequent wheezing were also confirmed by CO measures, which strongly correlated among mothers with reported number of cigarettes ($n=180$, $r=0.763$; $p<0.001$). The correlation between the number of cigarettes and the expired CO was less satisfactory amongst the few fathers who had performed it ($n=41$, $r=0.51$; $p<0.001$). The prevalence of frequent

rhinitis was increased also in children exposed to dampness in the inhabitation zone (13.9%) (OR=2.6, 95%CI 1.1–4.1) and to gas heating (31.7%) (OR=1.8, 95%CI 1.0–3.4). Having a pet (18%) and washing blankets at less than 60°C (63.5%) were inversely related to wheezing (OR=0.3, 95%CI 0.1–0.9 and OR=0.5, 95%CI 0.2–0.9, respectively).

Results were confirmed after including in the logistic model each clinical manifestation of atopic disease as a dependent variable and simultaneously all the early life risk factors, which had been found to be significantly related to these manifestations, as independent variables.

The OR associated with the joint exposure to *in utero* smoking and infantile colic was 4.2 in the case of wheezing and 9.4 in the case of diagnosed asthma.

Discussion

Our data show the involvement of early life influences in childhood manifestations of atopic disease but not in allergic sensitization to common allergens, except in the case of low fruit intake. The latter findings could be due to the fact that allergic sensitization usually develops in childhood (14), although it may arise already during intrauterine life (3,12,13).

Our data not only confirm previous results on early life influences upon allergy but also reveal new risk factors for its development. Known early life risk factors confirmed by our study were familial history of allergy, male gender, month of birth, anesthesia at delivery, prematurity, low birthweight, passive smoking, respiratory infections, and the type of heating (15–21), although contradictory results exist for some of these factors (22–24). Early exposure to infections has been shown to protect against atopic disease by promotion of T-helper 1 responses (22). Prematurity has been found to be a risk factor for asthma but not for eczema (23) and food allergy (24). The already known relationship of early smoke exposure to wheezing was strengthened in our study by the fact that maternal smoking was objectively assessed at the period of the survey using expired CO. In agreement with previous results (25), paternal smoking was not a risk factor of any atopic disease in our study, presumably because fathers do not usually smoke in the presence of the child for sufficiently long periods. Our data support also maternal phenotype influences in the inheritance of asthma and allergy, overall in boys (26). Finally, in agreement with previous results, our data show that early exposure to pets, including cats, might modulate

immune mechanisms and reduce the risk of allergy (27). Confirming previous results ensured the credibility of our data.

New evidence on unrecognized or unknown risk factors for the development of atopic symptoms was provided in our study by examining more in detail pregnancy and birth events and relating such events to SPT positivity, which had never been carried out previously. Threatened abortions and fetal health complications were related to clinical manifestations of atopic disease but not to SPT positivity in our study, independent of the sex of the child. The adjustment on sex was necessary because it is known that the male fetus is more vulnerable than the female fetus and that allergy is more frequent in boys. Recent studies have had similar findings but only in the case of asthma (28,29). Furthermore, infantile colic was identified as an additional early life factor for frequent wheezing and diagnosed asthma in our study and the risk associated with it increased when the mother had smoked during pregnancy. There exists previous evidence that parental active smoking, an established risk factor for wheezing and asthma, has an effect also on infantile colic (30) but no investigation had ever related infantile colic with asthma. Infantile colic is thought to result from the contraction of smooth muscles in the abdomen, which causes are presently only hypothesized. As smooth muscles are found also in the bronchi, our findings seem consistent with the hypothesis that infantile colic might be an early marker of the individual susceptibility to develop bronchial constriction, a main feature of wheezing and asthma, but further studies are needed.

Skin-prick test positivity was not related to early life influence in our sample. This is consistent with the fact that up to now the only established risk factor for allergic sensitization in early life is allergen exposure (4). On the contrary, total IgE have been related to early life risk factors other than allergenic exposure, such as progesterone intake (4) and head circumference at birth (5). The latter might depend on the underdevelopment of the thymus, which participates to IgE production, due to disproportionate fetal growth. Head circumference at birth was not available in our study, but other markers of fetal growth like birthweight or prematurity were not related to skin prick test positivity in our sample. This may reflect different roles played by SPT positivity and total IgE production in the allergic cascade.

In order to better interpret our findings, it seems worthwhile to acknowledge and discuss the study's potential, which include sample size,

causality assessment, recall bias and allergen choice. The sample can be considered as representative due to the selection method employed. Furthermore, it provides a 80% power to detect a difference in the prevalence of atopic disease among all children of 10% vs. 20% according to the absence or the presence of a risk exposure. In spite of the cross-sectional study design, causality is also supported in our study by the fact that temporality, plausibility and coherence criteria were satisfactorily fulfilled. In addition, recall bias was reduced in our study by the fact that young children were interviewed. Lastly, only major allergens were tested because of the age of the children. However, they were the allergens frequently used in population screening. As a result, the prevalence of SPT positivity we found is similar to that observed in a larger sample of Italian children (31).

How early life events influence the development of IgE-mediated allergy in the offspring is not known and deserves further investigations. IgE-mediated allergy is primarily an inflammatory disorder orchestrated, through the action of various factors, by Th2 lymphocytes, which priming occurs early in life (2). On the basis of the immune response of fetal and newborn mice, immaturity has been postulated to prevent tolerance to antigens in the neonatal period (32). Similarly, under-nutrition has been implicated in IgE production (5). However, other factors seem to be involved in clinical manifestations of atopic diseases that have a more multifactorial etiology than allergic sensitization. Early life events might act directly on target organs, such as in the case of threatened abortions, which have been put in association with both child's asthma and mother's bronchial hyperresponsiveness (33) during pregnancy.

The finding of the role of antenatal and perinatal factors and the finding that male gender is a predictor of allergic sensitization may suggest the presence of gender-related processes of various origins starting already in early life in the development of allergy (34), which needs to be further explored. The confirmation of a maternal effect (34,35) is also relevant in this context. Events early in life seem critical, as the development of IgE-mediated allergy would be fostered by the mother's strained immune relationship with the fetus.

In conclusion, our findings support the hypothesis that atopic symptoms could be a manifestation of the interaction between genes and early life events other than allergen exposure. The relative contributions of such factors are not yet clear and need to be further investigated.

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