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Longitudinal predictors of airway responsiveness to distilled water: the role of atopy and maternal smoke exposure

M. Studnicka*, B. Roithner**, C. Gartner**, S.T. Weiss+, M. Neumann*, T. Frischer*

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ABSTRACT: Airway responsiveness is an objectively measurable clinical trait related to the presence of asthma. Although risk factors for this trait have been evaluated cross-sectionally, little is known about its longitudinal predictors.

A population cohort of 539 children, aged 8 yrs at the start of follow-up, underwent 3–7 bronchial challenge tests spaced at 3–9 month intervals. Airway responsiveness was assessed by a single-step distilled water challenge. To investigate responsiveness as a continuous trait, the ratio of the postchallenge to prechallenge forced expiratory volume in one second was calculated. A child's repeated ratios were then regressed on the time of follow-up. The resulting child-specific regression coefficient was the outcome variable to assess longitudinal predictors of airway responsiveness (AR).

Results were based on 2,267 repeated challenge tests, and indicated an overall decrease in responsiveness. Children with a diagnosis of asthma (mean±SD, longitudinal change in AR·yr^{-1}: -0.060±0.149), those with a positive skin-prick test (-0.018±0.106) and those with reported exposure to maternal smoking (-0.004±0.083) demonstrated increased airway responsiveness over time. All of these changes in airway responsiveness were found to be significant in multiple linear regression analysis ($p<0.05$). Stratified analysis further indicated that the effect of maternal smoking was observed primarily in nonatopic children and was greatest at an exposure level of Š10 cigarettes·day^{-1}.

In conclusion, atopy and exposure to maternal smoking can predict longitudinal change in childhood airway responsiveness.

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*First Internal Dept, Centre for Pulmonary Disease, Vienna, Austria. **University Children's Hospital, Vienna, Austria. +Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

Correspondence: T. Frischer
University Kinderklinik Wien
Währinger Gürtel 18–20
A-1090 Wien
Austria
Fax: 43 1 40400 3189

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Airway responsiveness in childhood has been reported to decrease with age [1–3]. In the past, this evidence has been based on cross-sectional studies, while more recently, longitudinal studies have confirmed this finding. The age-related changes in responsiveness have been attributed to parallel changes in airway geometry and breathing pattern [4, 5]. FORASTIERE *et al.* [1] reported two surveys with methacholine provocation tests separated by 3.5 yrs. A marked decrease in the prevalence of responsiveness was seen, but children with atopy were observed to retain responsiveness. BURROWS *et al.* [2] similarly reported on four repeated methacholine tests and noted an overall de-crease in airway responsiveness, while this was less pronounced in subjects with positive skin-tests or elevated serum immunoglobulin (Ig)-E. Although these two studies presented longitudinal evidence, they did not analyse airway responsiveness as an individual characteristic with repeated measurements recorded for the same subject. The longitudinal comparison of frequencies of positive tests between children with different airway responsiveness at the start of follow-up might still not account fully for the within-subject development of this trait.

Airway responsiveness has been found to be repeatedly and consistently related to atopy in a number of cross-sectional studies [3, 6]. This relation was further confirmed in cohort studies. For the data presented by FORASTIERE *et al.* [1], and BURROWS *et al.* [2], atopy was the strongest predictor of persistently increased responsiveness. This association has also been seen in genetic linkage studies and a shared genetic region for airway responsiveness and atopy has been hypothesized [7].

Exposure to maternal smoking has been less convincingly linked with increased responsiveness during childhood. Some cross-sectional studies have reported such an association, while others have failed to demonstrate it [8–11]. FORASTIERE *et al.* [1, 11] reported a three-fold increas-ed prevalence of airway responsiveness in females exposed to maternal smoking, but could not repeat this finding at the second survey when children's mean age was 13 yrs. This observation indicates that the influence of maternal smoking might decrease as the child's age increases. YOUNG *et al.* [12] however, reported risk estimates of similar magnitude when investigating the influence of a family history of asthma and parental smoking on airway responsiveness in healthy infants.

This study investigated, in a population cohort of children, whether atopy, as defined by skin-prick test and maternal smoking are risk factors for increased airway responsiveness. For the purpose of this analysis, the outcome variable studied was a child's within-subject longitudinal change in responsiveness, based on at least three repeated tests.

Methods

Study population

The original aim of the study was to investigate the effects of air pollution (NO_2, SO_2) on lung function and airway responsiveness at four sites in Lower Austria. The sites were selected on the basis of past ambient pollution records and, as previously reported, were homogeneous with regard to demographic background characteristics [13]. Furthermore, Austrian ambient air-quality standards for NO_2 and SO_2 were never exceeded during the study period. At each site, public primary schools were sampled for participation.

The study was designed as a dynamic cohort study, *i.e.* at each year children entered and left the cohort. In detail, during the first year, children in their second, third or fourth grade of primary school entered the cohort and those in the fourth grade left the cohort at the end of the year. During the second and third years, children in grade 2 entered and children in grade 4 left the study cohort. It was originally planned to perform three repeated surveys each year (autumn, winter and spring); however, for financial reasons only two surveys (winter and spring) were performed in the second and third year of study. An individual child was therefore followed for 1, 2 or 3 yrs; and should have completed from 2–7 tests for airway responsiveness. For the purpose of the present analysis, *i.e.* to obtain a stable estimate of the longitudinal change in responsiveness, only children with at least three tests were considered. Therefore, children who entered during year 3 were excluded *a priori.* Ethical approval for the study was obtained from the Lower Austrian board of school authorities and for each participating child a parent or guardian gave informed, written consent.

Questionnaire and skin-testing

At the beginning of each year of study, a standard parental questionnaire [14] was completed. The questionnaire established whether asthma or wheezy bronchitis had been diagnosed or shortness of breath had been noted during the preceding 12 months. Asthma medication was only questioned in children reporting a clinical diagnosis of this disease. At the time of measurement of airway responsiveness, it was ascertained whether children had been ill during the preceding 2 weeks. If the illness was associated with a cough, a recent respiratory episode was assumed. At the beginning of each study year, it was also ascertained whether the child had been passively exposed to cigarette smoke as a result of maternal smoking. The number of cigarettes smoked in a child's home during the last 12 months was determined. A child's exposure to maternal smoking was estimated as the mean number of cigarettes reported for the complete follow-up.

Skin-prick testing for allergy was always conducted in January, February or March during a child's first year of study. The response to histamine (10 $mg \cdot mL^{-1}$), 0.9% NaCl and seven prevalent allergens (cat dander, dog dander, house-dust mite (*Dermatophagoides pteronyssinus*), birch, raygrass, orchard grass and *Alternaria*) (ALK Laboratories, Copenhagen, Denmark) was determined. The antigens chosen to identify atopy were those being used for screening subjects in clinical practice and included the most prevalent in the study area. Extracts were placed on the skin of the forearm, and the site was pricked with a standard 1-mm prick lancet. The maximal wheal diameter was read after 10 min. Atopy, when defined as a binary variable, was considered present when at least one allergen wheal response Š histamine was measured. As described by BURROWS *et al.* [6], continuous variables on the child's response to indoor or outdoor allergens were also derived. To determine the response to indoor allergens, the wheals (in mm) were summated for cat dander, dog dander and house-dust mite and the sum was divided by 3. For atopy to outdoor allergens, the response to birch, raygrass, orchard grass and *Alternaria* was summated and divided by 4.

Assessment of lung function and distilled water airway responsiveness

Up to seven measurements of prechallenge lung function and responsiveness to distilled water were recorded for each participant (see above). Lung function was measured with a heated linear pneumotachygraph (Jaeger Würzburg, Germany) in accordance with American Thoracic Society criteria [15]. The greatest prechallenge and postchallenge forced expiratory volume in one second (FEV_1) from an appropriate manoeuvre was always chosen for analysis. When prechallenge bronchoconstriction (defined as FEV_1/forced vital capacity (FVC) <0.70) was detected, children were exempted from challenge testing. The protocol consisted of 10 min of inhalation of ultrasonically nebulized distilled water [16]. While breathing tidally, children were connected with the nebulizer *via* an expiratory tube and an interconnected three-way valve to prevent rebreathing. A positive challenge test was defined as a Š10% fall of prechallenge FEV_1. To evaluate responsiveness as a continuous trait, the ratio of postchallenge to prechallenge FEV_1 was calculated [13]. This measure can be derived from the more commonly used expression of "percentage fall in FEV_1", however, the postchallenge to prechallenge FEV_1 ratio offers the advantage of being easily converted on a logarithmic scale.

Data analysis

Children with incomplete follow-up were compared with those who completed three or more challenge tests. The longitudinal change in airway responsiveness was evaluated as a continuous trait. Thus a child's repeated postchallenge-to-prechallenge FEV_1 ratios were regressed on the time of follow-up. The resulting child-specific regression coefficient (change in airway responsiveness ratio$\cdot yr^{-1}$) was the outcome variable. Predictors of responsiveness were investigated with linear regression models. The variance (s^2) derived from a child's repeated postchallenge to prechallenge FEV_1 ratios was used as a measure to indicate within-subject variability in this trait [17].

A child's characteristics at the start of follow-up, including sex, height and prechallenge lung function (forced expiratory flow at 25, 50 and 75% of FVC (FEF_{25}, FEF_{50}, FEF_{75}, respectively), and FVC), were assessed. However,

FEV_1 was not entered into the regression equation, given the correlation between responsiveness and FEV_1 on pure statistical grounds. Instead, subgroups of children according to quartiles of prechallenge FEF_{50}/FVC were investigated. When airway responsiveness at baseline was assessed as a predictor of the change in responsiveness, only children with at least four repeated tests were included.

Other possible predictors of the longitudinal change in responsiveness, such as atopy, exposure to maternal smoking and the presence of respiratory symptoms, were subsequently analysed. Atopy and maternal smoking were fitted as dichotomous and continuous variables, and multivariate and stratified regression models were considered. An interaction term for atopy and maternal smoking was also included. To assess the validity of the results, analysis was repeated in a number of ways (see Results).

Results

Study population characteristics

The proportion of potential participants, as verified by school statistics, whose parents gave consent was 83% in yr 1, 79% in yr 2 and 79% in yr 3. For children who were eligible but did not take part in the study, no information on respiratory symptoms was obtained. Out of 705 children who entered during yr 1 or 2 and could therefore have completed three challenge tests, 23% contributed only one or two tests. These 166 children were not found to differ with regard to asthma (3% *versus* 3%; p=0.85), atopy (13% *versus* 7%; p=0.12), presence of maternal smoking (40% *versus* 31%; p=0.12), or a positive challenge test at baseline (10% *versus* 9%; p=0.80) from the 539 children with complete follow-up.

Table 1. – Consistency of responder status for distilled-water airway responsiveness*, stratified by number of tests during follow-up

	Number of airway challenge tests				
Responder status	3	4	5	6	7
Always positive	3 (1)	2 (2)	0 (0)	0 (0)	0 (0)
Never positive	182 (82)	101 (77)	87 (91)	21 (62)	33 (59)
Variable	36 (16)	29 (22)	9 (9)	13 (38)	23 (41)
All	221	132	96	34	56

Values are numbers, with percentages in parenthesis. *: presence of distilled-water airway responsiveness, *i.e* fall in the forced expiratory volume in one second (FEV_1) by Š10%.

Consistency of airway responder status and variance of repeated challenge tests

The consistency of a positive airway challenge was evaluated on the basis of the number of completed tests (table 1). Of 353 children who completed either three or four tests, five (1.4%) had consistently positive results and 283 (80%) had consistently negative results. As expected, the proportion of variable responders generally increased with the number of measurements and was 41% in children with seven tests.

As an index of within-subject variability of airway responsiveness, the variance in each child's repeated tests was calculated. This within-subject variance was compared with regard to a child's diagnosis of asthma, atopy and presence of maternal smoking. For children with asthma (p=0.06 as tested by t-test), as well as for those with atopy (p=0.08 as tested by t-test), the within-subjects variance of airway responsiveness was increased threefold, while for children with exposure to maternal smoking a two-fold greater variance (p=0.04 as tested by t-test) was seen.

Longitudinal change in airway responsiveness

Overall, the proportion of positive challenge tests decreased during follow-up (table 2). The population mean of the longitudinal change in airway responsiveness, estimated for 539 children, indicated a significant decrease for the entire group (p=0.05 as tested by the t-test) (table 2). This overall decrease in responsiveness was more pronounced when only nonasthmatic and nonatopic children were considered (p=0.004 as tested by t-test). When investigating the longitudinal change in airway responsiveness, baseline lung function (FEF_{25}, FEF_{50}, FEF_{75} and FVC) recorded at a child's first test was not a significant predictor. For the FEF_{50}/FVC ratio, a composed measure of airways obstruction categorized into quartiles, no significant result was seen either. This was also the case for airway responsiveness at baseline. Similarly, no significant estimate was observed in association with a child's sex (table 3).

Table 2. – Number of tests positive for airway responsiveness* to distilled water challenge, stratified by survey and time of follow-up

			Number (%) of positive tests at indicated survey						
Follow-up (no. of children†)	Grade at start	Age at start‡ yrs	1st (Oct–Dec 1987)	2nd (Jan–Mar 1988)	3rd (Apr–Jun 1988)	4th (Jan–Mar 1989)	5th (Apr–Jun 1989)	6th (Jan–Mar 1990)	7th (Apr–Jun 1990)
During yrs 1, 2 and 3 (101)	2nd	7.8 (0.4)	15 (15.6)	12 (12.6)	4 (4.3)	9 (9.4)	6 (6.7)	7 (8.0)	7 (7.6)
During yrs 1 and 2 (139)	3rd	8.7 (0.5)	10 (7.4)	6 (4.8)	1 (0.9)	7 (5.8)	2 (1.6)		
During yr 1 (157)	4th	9.6 (0.8)	15 (9.5)	11 (7.0)	11 (7.0)				
During yrs 2 and 3 (142)	2nd	8.1 (0.6)#				13 (9.8)	10 (7.3)	5 (3.9)	14 (11.4)

*: airway responsiveness (AR) is defined as a fall in the forced expiratory volume in one second (FEV_1) by Š10% following distilled-water challenge. †: these numbers indicate children who contributed at least three AR tests during follow-up. However, at each survey a few children did not attend and therefore the percentages of positive tests do not correspond exactly with the number of children with at least three AR tests. ‡: mean (SD). #: children entering the cohort in yr 2 were 3 months older, given that no autumn survey was conducted in this year.

Table 3. – Baseline and yearly longitudinal change in airway responsiveness (AR)

Characteristic	n	Baseline AR*	Longitudinal change in AR yr^{-1}	p-value†
All children	539	0.966 (0.057)	0.004 (0.080)	
Sex				
Male	264	0.967 (0.059)	0.001 (0.077)	NS
Females	275	0.964 (0.056)	0.009 (0.082)	
Asthma				
Present	15	0.893 (0.093)	-0.060 (0.149)	0.001
Absent	518	0.968 (0.055)	0.006 (0.076)	
Wheezy bronchitis				
Present	71	0.944 (0.077)	0.004 (0.125)	NS
Absent	461	0.969 (0.053)	0.004 (0.070)	
Shortness of breath				
Present	26	0.900 (0.100)	0.027 (0.161)	NS
Absent	504	0.969 (0.053)	0.002 (0.074)	
Recent respiratory episode at any AR test				
Present	193	0.958 (0.064)	0.016 (0.087)	0.001
Absent	346	0.970 (0.053)	-0.002 (0.075)	
Atopy (Š1 allergen)				
Yes	64	0.949 (0.080)	-0.018 (0.106)	0.008
No	419	0.968 (0.054)	0.010 (0.071)	
Maternal smoking (Š1 cigarette·day^{-1})				
Yes	212	0.967 (0.063)	-0.004 (0.083)	0.034
No	324	0.965 (0.053)	0.010 (0.077)	

Values are shown as mean (SD). *: AR to distilled water, expressed as the ratio of the postchallenge to prechallenge forced expiratory volume in one second (FEV_1). †: derived from comparisons of the longitudinal change in AR between children with and without the given characteristic, adjusted for sex and height at baseline. NS: nonsignificant.

Asthma, atopy, exposure to maternal smoking and the longitudinal change in airway responsiveness

For 15 children with a diagnosis of asthma, an increase in airway responsiveness was noted, while no such effect was seen in association with wheezy bronchitis or shortness of breath (table 3). Children with a recent respiratory episode prior to any challenge test demonstrated a significant decrease in responsiveness (p=0.01). Atopic status significantly predicted the longitudinal change in responsiveness (tables 3–5). When atopy was considered as a graded response (*i.e.* the mean allergen wheal size in mm), a significant relation was only seen for indoor (p=0.04) but not for outdoor allergens (p=0.11) (table 4). Children with reported exposure to maternal smoking at any time also demonstrated a significant increase in responsiveness (p=0.034). This effect was confirmed when maternal smoke exposure was calculated as the number of cigarettes smoked at home by a child's mother (p=0.023).

When atopy and maternal smoking were included in the same model, the coefficient associated with smoking indicated an increase in responsiveness that fell short of statistical significance (p=0.10). Consistent results were obtained when atopy and maternal smoking were fitted as binary and continuous explanatory variables. Stratified analysis further showed that the effect of maternal smoking on airway responsiveness was seen primarily in nonatopic children (table 5). Atopy to indoor allergens had an effect of similar magnitude, irrespective of a child's exposure to maternal smoking (table 5). As expected, an interaction term for atopy and maternal smoking was found to be nonsignificant.

Further analysis of maternal smoking in nonatopic children demonstrated a dose-response relation. While this relation was not significant in children reportedly exposed to <5 cigarettes·day^{-1}, it was of borderline significance in those exposed to 5–10 cigarettes·day^{-1} (p=0.11) and was most pronounced in those exposed to Š10 cigarettes·day^{-1} (p=0.014). The corresponding regression coefficients showed an increase in magnitude in parallel with the reported level of passive smoke exposure.

Validity analysis

Consistent results were obtained for atopy and maternal smoking, when using the log-transformed postchallenge to prechallenge FEV_1 ratio as the outcome. Inclusion of baseline lung function or "a recent respiratory episode at any challenge" as a potential confounding variable had no effect on regression estimates for atopy and maternal smoking. Weighted analysis, when taking into account the number of tests completed by each child, also produced consistent data. When the inverse of the variance of a

Table 4. – Association between atopy and yearly longitudinal change in airway responsiveness

	Regression coefficient* (SE)	p-value
Atopy (Š1 allergen)	-0.0022 (0.0008)	0.008
Atopy (mean wheal size in mm) to indoor allergens	-0.0126 (0.0060)	0.036
Atopy (mean wheal size in mm) to outdoor allergens	-0.0117 (0.0074)	0.11

*: derived from three models, adjusted for sex and height at baseline.

Table 5. – Effect of atopy and maternal smoking on the yearly longitudinal change in airway responsiveness

Strata	Regression coefficient* (SE)	p-value
Atopy present		
MS (Š1 cigarette·day^{-1})	0.010 (0.028)	NS
MS (no. of cigarettes·day^{-1})	0.032 (0.022)	NS
Atopy absent		
MS (Š1 cigarette·day^{-1})	-0.014 (0.007)	0.04
MS (no. of cigarettes·day^{-1})	-0.015 (0.005)	0.006
MS present		
Atopy (Š1 allergen)	-0.015 (0.017)	NS
Atopy (mean wheal size in mm) to indoor allergens	-0.012 (0.013)	NS
Atopy (mean wheal size in mm) to outdoor allergens	-0.002 (0.013)	NS
MS absent		
Atopy (Š1 allergen)	-0.035 (0.012)	0.005
Atopy (mean wheal size in mm) to indoor allergens	-0.014 (0.006)	0.03
Atopy (mean wheal size in mm) to outdoor allergens	-0.018 (0.009)	0.04

*: regression coefficient derived from multivariate models, taking into account sex and height at baseline. MS: maternal smoking; NS: nonsignificant.

child's repeated tests for responsiveness was the weight factor, the regression coefficients for atopy and maternal smoking were smaller and nonsignificant, but of the same direction. This should be attributed to the marked differences with regard to the within-subject variance of a child's repeated tests for airway responsiveness (see above). Extended analysis after the inclusion of 88 positive challenge tests (see Methods), originally excluded because of prechallenge bronchoconstriction, resulted in similar estimates for the effects of atopy and maternal smoking. When, 15 children with asthma were excluded to control for any effect due to current medication, these estimates were also found to be consistent. Furthermore, similar results for atopy and maternal smoking were obtained following exclusion of 192 children reporting a recent respiratory episode at any challenge test.

Discussion

This study reported a longitudinal decrease in distilled-water airway responsiveness in a population cohort of children. Despite this overall trend, the opposite trend was seen in children with asthma or atopy. In addition, exposure to maternal smoking was independently associated with a longitudinal increase in responsiveness. This effect of maternal smoking was seen primarily in nonatopic children and greater exposure was associated with a more pronounced effect on responsiveness.

Airway responsiveness in childhood has been observed to decrease with age, but the evidence documenting this decrease has until recently been cross-sectional [3, 18]. A few follow-up studies have recently become available [1, 2]. BURROWS *et al.* [2] reported a significant overall de-crease in methacholine responsiveness from the age of 9–15 yrs. However, the proportion of children with severe responsiveness increased from 8.5% at the age of 9 yrs to 11% at 15 yrs. A cohort study from Italy [1] reported methacholine challenge tests in 7–11 yr-old children who were retested after 3.5 yrs. Between the two visits, the proportion of children with a positive challenge test decreased from 15.4% to 11.3%. Comparison of these studies with the present findings suggests that the relatively brief follow-up may have prevented the observation of a more pronounced change in responsiveness in all children. However, those followed for 3 yrs demonstrated a decrease in positive tests from 15.6 to 7.6% (table 2). Methacholine challenge has been shown to be more sensitive than distilled-water challenge for diagnosis of asthma [19]. Thus, the expectedly lower frequency of positive distilled-water tests at the start of follow-up could also have explained the smaller decrease in responsiveness. Nevertheless, a child's reported respiratory episode prior to any challenge test was a significant predictor of decreased responsiveness, indicating that respiratory infections may play a role in the childhood development of this trait. Whether the longitudinal changes in distilled-water responsiveness were related to changes in bronchial inflammation, airway geometry or altered breathing pattern, or some combination of these factors was not addressed by the present investigation.

No relationship was found between lung function or airway responsiveness at baseline and the change in responsiveness during follow-up. BURROWS *et al*. [2] report-ed a significant association between responsiveness and spirometry assessed at the end of follow-up. FORASTIERE *et al.* [1] did not report longitudinal results on airway responsiveness and lung function but noted significant cross-sectional associations. In a previous analysis, a cross-sectional association was also observed between lung function and level of airway responsiveness [3]. Given the absence of a longitudinal relation, it is hypothesized that the results of single-step distilled-water challenge are only loosely correlated with lung function. Because of either its postulated direct action on bronchial smooth muscle cells or its repeated administration, methacholine responsiveness may be more closely related to airway geometry.

Follow-up data have shown considerable within-subject variability of repeated measurements of responsiveness [2, 20]. REDLINE *et al.* [20] reported on the cold-air responsiveness of 179 subjects, each of whom completed between two and five tests. These authors observed that 3% of subjects had consistently positive results, 24% had variably positive and 73% had consistently negative results. FORASTIERE *et al.* [1] described the reproducibility of methacholine responsiveness results in two surveys: 4.7% of subjects demonstrated severe responsiveness on both occasions, while 41% did not respond on either occasion. BURROWS *et al*. [2] reported on four repeated tests: 4.0% of subjects were always "at least moderately responsive",

while 66% were consistently nonresponsive. In the present study, 1.4% of children completing either three or four distilled-water challenge tests were consistently positive and 80% were consistently negative. Taken together, these follow-up studies document considerable within-subjects variability in airway responsiveness.

To characterize within-subject variability in responsiveness, the variance in repeated challenge tests was chosen. Based on this index, children with atopy and asthma, but also those with exposure to maternal smoking, demonstrated greater variability. This finding indicates that not only airway responsiveness itself, but also the variability in this trait might be related to airway inflammation. However, the proportion in variance directly attributable to measurement error can only be determined with short-term repeated measurements of airway responsiveness, which were not available for this study.

Besides a reported diagnosis of asthma, atopy was the strongest predictor of increased responsiveness. For atopy as a graded response, a significant relation was found with indoor and not with outdoor antigens. Studies have repeatedly demonstrated that atopy is strongly associated with childhood airway responsiveness [1–3, 6, 13]. Indoor allergens, especially those from house-dust mites, have been speculated to be the most important exposure affecting the development of asthma in childhood [21].

Maternal smoking was also a risk factor. Some cross-sectional studies have found a positive association between responsiveness and passive smoking [9–11], whereas others have found no such relationship [3, 8, 22]. YOUNG *et al*. [12] observed an association between prenatal smoke exposure and postnatal responsiveness to histamine. Thus, passive smoke exposure may have an effect even during prenatal growth. Decreased lung function has also been associated with passive smoke exposure and recent evidence indicates that this association may develop very early in life [23]. MARTINEZ *et al*. [10] reported increased responsiveness due to passive smoke exposure in 9-yr-old males [10]. In the two cross-sectional surveys reported by FORASTIERE and co-workers [1, 11], passive smoking was a significant risk factor in the latter survey but not in the former. These observations indicate that the association between passive smoke exposure and airway responsiveness may be dependent on age. This effect of age may mediate: 1) the time a child spends close to their mother, 2) changes in airway geometry, or 3) maturation of the immune response. Furthermore, the relation between passive smoke exposure and airway responsiveness may also be subject to a "healthy passive-smoker" effect [24]. Whether smoking in the household by other family members should have increased the estimate associated with passive smoke exposure remains at stake. A recent study into current asthma and wheeze in relation to environmental tobacco smoke has demonstrated that estimates based only on maternal smoking can underestimate true exposure [25]. With regard to the combined effect of atopy and maternal smoking a negative interaction was seen. This might be related to the fact that a longitudinal increase in responsiveness as well as greater within-subject variability in responsiveness were observed for children with the same characteristics. Consequently, the effect of maternal smoking might be blurred in children with atopy, because of their greater variability in responsiveness.

A child's reported respiratory episode prior to challenge testing was found to be significantly related to decreased responsiveness during follow-up. Given that a greater number of respiratory episodes was observed at the beginning of a child's follow-up [13], this decrease in longitudinal responsiveness could also be interpreted as a rebound effect following greater responsiveness during such an episode.

In conclusion, follow-up with 2,267 measurements of distilled-water airway responsiveness was reported in a population-based sample of 539 children. For nonatopic children, responsiveness decreased significantly with age, while the opposite trend was seen for atopic children. Moreover, repeated measurements for airway responsiveness in the same subject demonstrated considerable within-subject variability. Besides atopy, maternal smoke exposure was a significant risk for increased airway responsiveness.

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