

Original article

Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years

Background: The role of passive smoking for allergies and asthma in children above the age of 3 years remains unclear and possible interactive effects with parental allergies have not been formally evaluated in long-term studies. To examine the interaction of passive smoking and an allergic predisposition regarding allergic sensitization, allergic airway symptoms and respiratory infections during the first 10 years of life.

Methods: In a prospective multicenter birth cohort study with 1314 recruited children in Germany, we assessed serum immunoglobulin E against common allergens at seven time points, and parental smoking and respiratory symptoms annually by using questionnaires. Longitudinal analyses were performed using generalized estimating equation models (stratified by parental allergy status).

Results: During the first 10 years, 18% of the children were exposed to regular maternal smoking since pregnancy, 43% to irregular maternal or only paternal smoking. Among children with two allergic parents, a mother who smoked regularly significantly increased the odds for allergic sensitization (adjusted OR 4.8, 95% CI 1.3–18.2) and wheezing (adjusted OR 5.7, 95% CI 1.7–19.0) in her child compared with children who were never exposed. For those with only one allergic parent, the odds were doubled and also statistically significant, whereas in children without allergic parents maternal smoking had no effects. There was no association of maternal smoking with allergic rhinitis or respiratory infections.

Conclusions: Our results suggest that regular maternal smoking is a strong risk factor for allergic sensitization and asthma symptoms during the first 10 years of life, but only in children with allergic parents.

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Key words: allergic sensitization; asthma; birth cohort study; interactive effects; longitudinal analysis.

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Background

A genetic predisposition presents the strongest risk factor for asthma and allergies (1, 2). However, the increasing prevalence in recent decades cannot be explained by genetics. Lifestyle, environmental factors and/or gene–environment interactions must play a role (3). To identify these largely unknown factors, longitudinal epidemiologic investigations should ideally start at birth, as allergies can start in infancy.

Postnatal parental smoking or maternal smoking during pregnancy seems to be associated with increased risk of asthma, wheezing, reduced lung function and respiratory infections in children aged <3 years (4–10), however, not with asthma symptoms in children aged 4–10 years (8), and not with allergic sensitization or allergic rhinitis (11–14). Recent genetic studies suggest

interactions of parental smoking with genetic polymorphisms increasing the risk of childhood asthma (15–18).

No evidence for an interaction between genetic predisposition to allergic disease and passive smoking for risk of asthma during the first 2 years of life was found in a Swedish study, although heredity and prenatal smoking had independently negative effects (13). In children beyond the age of 2 years, interactive effects between genetic predisposition and passive smoking regarding allergic disease have not been formally evaluated in longitudinal studies.

We examined, as primary outcome, the effects of pre- and postnatal passive smoking on the development of allergic sensitization during the first 10 years of life, and as secondary outcomes wheezing, allergic rhinitis and respiratory infections. *A priori*, we decided to stratify the data according to parental allergy status clarifying

possible interactive effects between the genetic predisposition and passive smoking.

Methods

Study design and participants

For the German birth cohort Multicenter Allergy Study (MAS), we recruited 1314 of 7609 infants born in six obstetric departments (Berlin, Duesseldorf, Freiburg, Mainz, Munich) in 1990. A detailed description of the stratified sampling scheme and the study subjects has been reported previously (19). Briefly, 6019 parents filled out a standardized family questionnaire on allergic diseases, relevant symptoms (current and ever wheezing, asthma, allergic rhinitis, eczema and food allergies) and tests. The questionnaire items indicating allergic diseases were validated by using the results of a Phadiatop test (Pharmacia CAP, Uppsala, Sweden) in a subsample of parents (20). Included in the study were only children with: (i) available umbilical cord blood immunoglobulin (IgE) values; (ii) ≥ 37 weeks of pregnancy; and (iii) ≥ 3 rd percentile of birth weight. Those with: (i) severe complications during birth; (ii) treatment on intensive care unit; or (iii) families with insufficient knowledge of the German language were excluded. Based on these criteria and written informed consent of the parents, we included 499 infants with a double positive family history (asthma, hay fever or eczema) and/or cord blood IgE values > 0.9 kU/l as children being at high risk, as well as 815 children selected at random from the remaining newborns with neither of these factors (19). The research protocol was approved by the ethics committee of the Charité University Medical Center, Berlin, Germany.

Outcome assessments

As an objective parameter, we measured serum specific IgE against nine food and aero-allergens (cow's milk, hen's egg, wheat, soy, mite, cat, dog, birch and timothy grass pollen) at age 1, 2, 3, 5, 6, 7 and 10 years (Pharmacia CAP). Allergic sensitization was defined if at least one specific IgE value was ≥ 0.35 kU/l, a definition used in previous studies examining the association between serum specific IgE and tobacco smoke exposure (21–23).

We applied stringent epidemiological definitions for the assessment of wheezing and allergic rhinitis (sneezing attack, or runny, blocked, or itchy nose in the absence of common cold) based on the widely used International Studies of Asthma and Allergies in Childhood (ISAAC) questions (1). Respiratory infections [rhinitis, sinusitis, pharyngitis, tonsillitis, laryngitis, bronchitis, otitis, pneumonia; coded using an extended version of the International Classification of Diseases (24)] were also subjectively assessed. All respiratory symptoms were recorded by parental questionnaires filled in before physical examination visits, five times during the first 2 years and annually thereafter until the age of 10 years.

Tobacco exposure assessment

We defined prenatal (*in utero*) tobacco exposure as *maternal* smoking during pregnancy assessed by using questionnaire at birth. We were able to determine cotinine (a major metabolite of nicotine) in the umbilical cord blood serum of 743 study children. Based on the evaluation of this subsample, we did not consider *paternal* smoking during pregnancy. We found the same low levels of cotinine in the cord blood serum of children where only the father smoked during pregnancy compared with those children where none of the parents reported to smoke: 12.3 (SD 38.6) vs 12.0 (SD 35.3)

ng/ml. However, if the mother reported smoking during pregnancy mean cotinine level in the cord blood serum was four times higher compared with the group of children where the mother reported not to have smoked.

Postnatal exposure was assessed by parental smoking at home. For each of the respective follow-up periods, we calculated a 'cross-sectional' tobacco smoke exposure variable with three categories: (i) never exposed; (ii) exposed only to father's smoking; (iii) exposed to mother's tobacco smoke (irrespective of father's smoking).

In the next step, we assessed the cumulative tobacco smoke exposure of the child until a specific year of age (prenatal plus postnatal tobacco smoke exposure). The 'cross-sectional' smoking data were cumulated over time until the respective follow-up (=age of child) and categorized according to the amount of exposure as described below. At least 50% of the follow-up data (i.e. nonmissing 'cross-sectional' exposure data) until a specific year of age had to be available in order to obtain a value for the cumulative tobacco smoke exposure variable, otherwise it was set as missing.

For the present longitudinal analyses, we defined four categories of tobacco smoke exposure: 1 = no parental smoking, 2 = only father smoked, 3 = mother smoked irregularly (irregular postnatal smoking or regular post- but not prenatal smoking) and 4 = mother smoked regularly (prenatal and regular postnatal smoking). Categories 3 and 4 were defined irrespective of father's smoking habits. 'Regular smoking' was coded if the mother reported smoking at a minimum of two-thirds of all available follow-ups. Category 4 also included 10 mothers who were regular postnatal smokers, but had missing values for pregnancy smoking. We made this assumption because 80% of all mothers who regularly smoked postnatally had also smoked during pregnancy.

Statistical methods

We used multiple longitudinal regression analyses – generalized estimating equation models – to assess the longitudinal effects of passive smoking exposure. These models take into account the correlation between repeated measures on the same individual and provide estimates when missing observations are unequally spaced (25, 26). The present analyses were based on a total of 6898 observations with data available for at least one of the four outcomes. The regression models were adjusted for possible study center effects (five centers) and variables that could influence the outcomes, defined *a priori* as follows: child's sex, birth weight (in grams), cord blood total IgE (< 0.35 vs ≥ 0.35 kU/l), siblings (categorical: older vs younger vs none), breast feeding duration (in weeks), educational level of parents (< 12 vs ≥ 12 years of schooling), pet exposure (dichotomous: dog, cat, rodent or bird vs none). Main interactions between tobacco smoke exposure and covariates were evaluated. The variables age of child and (age $\times$ age) were part of the models in order to estimate the change of the odds for the outcome as the children grew older.

Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were determined to estimate the odds for allergic sensitization, wheezing, allergic rhinitis and respiratory infections. The MAS study was enriched with relatively more children who had a family history of allergies and/or asthma, the most important risk factor for these diseases. Therefore, we decided *a priori* to stratify our analyses by parental allergy status, defined as having one or two parents who ever had asthma, allergic rhinitis and/or eczema (52% among all study children). The analyses were performed using SAS statistical software version 8.0 (SAS, Cary, NC, USA).

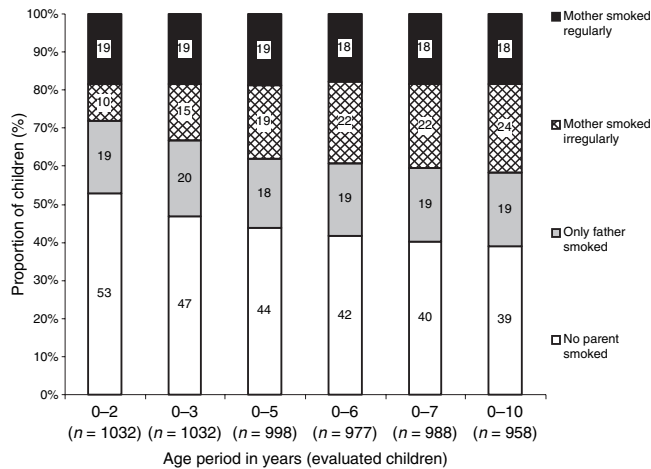


Figure 1. Exposure to parental smoking during the first 10 years of life ($n = 958$ – 1032). Parental smoking exposure was cumulated from pregnancy up to respective age.

Results

Participant description

A total of 958 (73%) children with valid data for the outcome and the exposure variables were included in the present analyses. Almost one in five children was exposed continuously to a regularly smoking mother during the first 10 years of life (Fig. 1). Allergic sensitization rose continuously up to 42%, whereas the proportion of children with current wheezing (in the last 12 months) remained relatively constant around 10% across different ages. At 10 years, 25% of all children experienced allergic rhinitis symptoms. The peak for respiratory infections was at the age of 3 years (Table 1).

Allergic sensitization

Exposure to regular maternal smoking increased significantly the odds for allergic sensitization compared with no tobacco smoke exposure, but only in children with allergic parents: adjusted OR 4.8, 95% CI 1.3–18.2

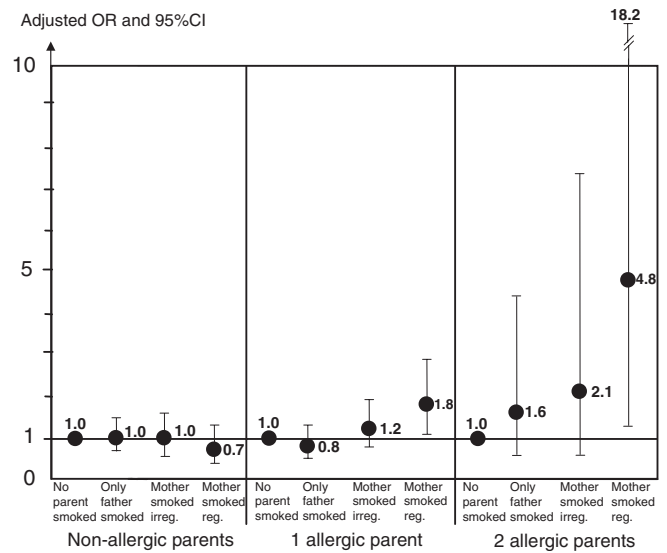


Figure 2. Association between parental smoking and allergic sensitization to common allergens during the first 10 years of life ($n = 958$). Odds ratios (OR) and 95% confidence intervals (95% CI) adjusted for age, sex, birth weight, breast feeding, siblings, pet exposure, parental education, cord blood IgE, study center (longitudinal analyses, stratified by parental allergic status). Reference categories were 'children with parents who did not smoke'.

(with two allergic parents) and adjusted OR 1.8, 95% CI 1.1–2.9 (with one allergic parent). Exposure to paternal or irregular maternal smoking also showed increased effect estimates (in children with two allergic parents), but lower than for regular maternal smoking and not statistically significant (Fig. 2). In children with non-allergic parents, there was no effect of parental smoking on the odds for allergic sensitization: adjusted OR 0.7, 95% CI 0.4–1.3 (Fig. 2). In the adjusted analysis of the total (unstratified) cohort, we found statistically significant effect modification between parental smoking and parental allergy status ($P = 0.040$), but not between parental smoking and other covariates.

The odds for allergic sensitization were significantly higher for boys vs girls among children having one allergic, (adjusted OR 2.1) and non-allergic parents

Table 1. Point prevalence of allergic and nonallergic outcomes for different time points during the first 10 years of life

Age at assessment (years)	Allergic sensitization* (≥ 0.35 kU/l)	Current wheezing (last 12 months)	Current allergic rhinitis (last 12 months)	Respiratory infections (≥ 3 episodes; last 12 months)
1	34/754 (5)	115/1112 (10)	66/1106 (6)	238/1120 (21)
2	81/661 (12)	74/1075 (7)	56/1075 (5)	221/1092 (20)
3	97/621 (16)	102/1049 (10)	111/1046 (11)	327/1051 (31)
5	181/647 (28)	103/984 (11)	152/984 (15)	265/1005 (27)
6	163/524 (31)	94/958 (10)	134/958 (14)	157/962 (16)
7	234/683 (34)	94/938 (10)	162/938 (17)	79/939 (8)
10	240/577 (42)	66/782 (8)	198/784 (25)	37/788 (5)

Values are expressed as n /total (%).

*Defined as positive serum specific IgE values to at least one allergen (mite, cat, dog, birch, grass, cow's milk, hen's egg, wheat and soy) at the respective time points.

(adjusted OR 1.7), for positive cord blood IgE ≥ 0.35 kU/L in children having one allergic parent (adjusted OR 1.7), and with increasing age regardless of parental allergy status (adjusted ORs between 1.6 and 2.0). No significant effects were seen for siblings, birth weight, breast feeding, pet exposure, parental educational level or study center.

Wheezing

Exposure to regular maternal smoking increased significantly the odds for wheezing compared with no tobacco smoke exposure, but only in children *with* allergic parents: adjusted OR 5.7, 95% CI 1.7–19.0 (with two allergic parents), adjusted OR 2.1, 95% CI 1.2–3.8 (with one allergic parent) and adjusted OR 1.2, 95% CI 0.6–2.4 (with non-allergic parents). In children with two allergic and those with non-allergic parents, the odds for wheezing were also increased for paternal smoking compared with no smoking exposure; however, this was only significant in children with non-allergic parents (Fig. 3).

In a further analysis, focusing on persistent or late-onset wheezing, the odds for wheezing were even more pronounced in the age group 4–10 years for children with two allergic parents and regular maternal smoking (adjusted OR 8.2, 95% CI 1.9–36.1), and similar as in the main analysis for children with one and non-allergic parents (data not shown). There was a trend for effect modification between parental smoking and parental allergy status, although not statistically significant: regarding wheezing in children aged 0–10 years

($P = 0.137$) and the subgroup aged 4–10 years ($P = 0.109$).

The odds for wheezing were significantly higher for boys *vs* girls in children who had one allergic parent (adjusted OR 1.7) and for positive cord blood IgE ≥ 0.35 kU/L in children who had two allergic parents (adjusted OR 2.7), but not with increasing age. No significant effects were seen for older or younger siblings, birth weight, breast feeding, pet exposure, parental educational level or study center.

Allergic rhinitis and respiratory infections

The odds for allergic rhinitis appeared not to be related to regular maternal smoking: adjusted OR 1.7, 95% CI 0.7–4.5 (with two allergic parents), adjusted OR 1.2, 95% CI 0.7–2.0 (with one allergic parent) and adjusted OR 0.8, 95% CI 0.4–1.3 (with non-allergic parents).

Similarly, the odds for respiratory tract infections were not related to regular maternal smoking stratified for parental allergy status: adjusted OR 1.4, 95% CI 0.7–2.8 (with two allergic parents), adjusted OR 1.2, 95% CI 0.9–1.8 (with one allergic parent) and adjusted OR 1.0, 95% CI 0.7–1.4 (with non-allergic parents).

Discussion

In this birth cohort study, exposure to passive smoking was strongly associated with allergic sensitization and asthma symptoms, but only in children with a genetic predisposition. For children with two allergic parents and a mother who regularly smoked the odds for either of the two conditions were increased about fivefold compared with children who were never exposed to tobacco smoke. In children with only one allergic parent and a mother who smoked regularly, the odds were increased about twofold. Maternal smoking had no effect in children with non-allergic parents.

Our findings challenge a systematic review on parental smoking and allergic sensitization in children that showed no effect of maternal smoking on allergic sensitization; however, the evidence reviewed was imperfect because of methodological weaknesses of the included studies (14). A recent study, published after the systematic review, showed a significant association of positive skin prick tests (house dust mites) with passive smoking only in children of allergic parents, but not in the group of children with non-allergic parents (21). We consider the longitudinal prospective assessments of tobacco smoke exposure as well as allergic sensitization (at seven time points during the first 10 years of life) as a particular strength of our study. *A priori*, we defined allergic sensitization by a positive IgE test to at least one of the nine most important allergens for children in Germany, because we did not want to exclude mono-sensitized children. However, most of the sensitized children in our

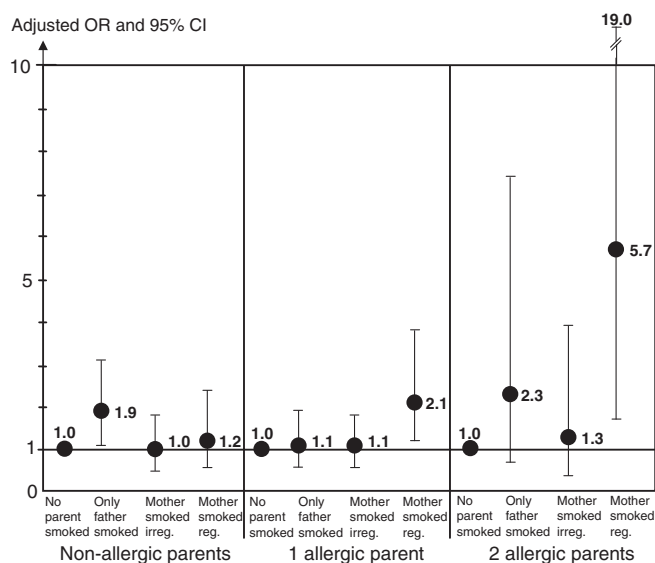


Figure 3. Association between parental smoking and wheezing during the first 10 years of life ($n = 958$). Odds ratios (OR) and 95% confidence intervals (95% CI) adjusted for age, sex, birth weight, breast feeding, siblings, pet exposure, parental education, cord blood IgE, study center (longitudinal analyses, stratified by parental allergic status). Reference categories were 'children with parents who did not smoke'.

study were poly-sensitized. For instance, 70% of all sensitized children had positive IgE tests to at least two allergens, 50% to at least three and 40% to at least four at the age of 10 years. At this time point, the three aero-allergens, house dust mite, grass or birch pollen, were responsible for almost all mono-sensitizations. A subgroup analysis that included only poly-sensitized children showed similar results as our main analysis with all sensitized children.

Regarding childhood wheezing, our analysis complements Strachan and Cook's systematic review (5). A novelty of our study was the formal evaluation of possible interactions between passive smoking and genetic predisposition over a period of 10 years, showing the highest odds for wheezing for regular maternal smoking combined with having two allergic parents.

We could not confirm the age-dependent effect on wheezing, found in an American birth cohort study up to the age of 6 years: a significant positive association with maternal smoking was found only for early-onset, transient wheezing (age ≤ 3 years), but not for persistent or late-onset wheezing (age > 3 years) (4). On the contrary, our subgroup analysis showed that regular maternal smoking and having two allergic parents had even more pronounced effects on wheezing in children aged 4–10 years (adjusted OR 8.2) than in the total cohort (adjusted OR 5.7). Another US birth cohort study up to 11 years of age showed significantly increased odds for wheezing for prenatal maternal smoking, but only in children < 3 years of age (OR 2.3). There were no effects of postnatal maternal smoking. As in our study, a longitudinal analysis approach was used; however, the interaction between maternal smoking and parental asthma was not statistically evaluated (8). The 10-year evaluation of a UK birth cohort showed that parental asthma and current parental smoking at the age of 4 years independently increased the odds for current wheezing at 10 years of age. Besides lacking a cumulative assessment of smoking exposure, possible interactions were not investigated (6). Parental smoking and allergic rhinitis were not associated in our study confirming results of previous investigations (11, 12, 14). However, this does not exclude a potential effect in adolescents, or adults.

Assessing parental smoking in the context of pregnancy or children is a sensitive issue and underreporting cannot be ruled out. Using self-report questionnaires instead of face-to-face interviews may have reduced such bias in our study. A possible weakness of our exposure assessment could be the lack of objective data for the follow-up period (for prenatal smoking we evaluated a subsample with cord blood measurements of cotinine, as reported under Methods). However, biomarkers, such as cotinine (measured in saliva or urine), with a relatively short half-life reflect *current* exposure over the past day or two, but cannot adequately represent *chronic* exposure. Furthermore, significant differences were reported for cotinine in

uptake, metabolism and excretion between individuals (27). Validation with indoor air nicotine measurements across several studies with preschool and school children demonstrated that parental questionnaires of smoking habits at home gave good estimates of passive smoking exposure (28, 29). Questionnaires seemed to provide sufficiently accurate qualitative information on tobacco smoke exposure; however, quantitative information should be interpreted with more caution (27).

The proportion of children in our study (61%) exposed to parental smoking, at least occasionally, during the first 10 years seems high but is well in line with adult smoking habits at the end of the 1990s in Germany. According to the representative national German health survey in 1998, 49% of men and 41% of women aged 30–39 years were current smokers, another 18% (men) and 20% (women) in the same age group reported to be ex-smokers (30).

Studies on health effects of passive smoking comparing maternal and paternal smoking showed consistent associations only with maternal but not paternal smoking (5, 7). Therefore, we defined 'regular' and 'irregular' maternal smoking exposure irrespective of paternal smoking. For wheezing, however, we found increased odds when only the father smoked in children with non-allergic parents and in those with two allergic parents (even higher odds, but not significant), whereas no effect was seen in children with only one allergic parent. This could have occurred by chance, or is an indication that the fact that only the father smoked might be a proxy of another, possibly socio-economic, factor influencing childhood wheeze, independent of the parental allergy status.

A decrease in the participation rate can be expected in long-term cohort studies. In many statistical analyses of observational studies only subjects with complete data are evaluated, whereas loss to follow-up and participants with missing values are not considered. For the present report, we used longitudinal analyses with the advantage that participants with missing data (at one or more but not all time points) remained in the analysis, by providing valid estimates even if missing observations are unequally spaced. This cannot completely rule out but reduce potential bias. A comparison of participants in the Danish National Birth Cohort with the source population suggested that the odds ratios for three chosen associations were not biased by nonparticipation (31).

Our epidemiologic findings raise the question of candidate genes for asthma or allergic disease that might be affected by tobacco smoke exposure. Genetic analyses in 433 Mexican children and their biologic parents found, only in children *with* a smoking parent, a statistically significant association between the risk of asthma and two highly associated single nucleotide polymorphisms in an arginase isoform (17). Arginases may contribute to asthma pathogenesis through various

mechanisms, including inhibition of nitric oxide (NO) generation, leading to airway remodeling (32). Tobacco smoke stimulates inflammatory cells in the airway (33), and can lead to decreased bronchodilatory NO, one of the possible mechanisms for synergistic effects with arginase activity (34).

Lack of glutathione S transferase enzyme isoform M1 allele combined with exposure to current passive smoking in 9- to 11-year-old children showed significantly higher odds for current asthma (OR 5.5), wheeze (OR 4.7) or shortness of breath (OR 8.9) compared with children who were isoform M1 positive and not exposed (16). However, a possible weakness in many genetic studies on asthma or allergies is the cross-sectional or retrospective assessment of tobacco smoke exposure, particularly for pregnancy or early childhood, instead of prospective assessments, which are less prone to bias.

Conclusions

Exposure to regular maternal smoking increased the odds for developing antibodies against allergens and for

wheezing up to the age of 10 years, but only in children with allergic parents. This longitudinal study was the first to formally evaluate the interaction between passive smoking and genetic predisposition for allergic outcomes in children beyond infancy. Our findings should encourage other long-term birth cohort studies to examine this possible interaction. The underlying mechanisms may be elucidated by further research of genetic variants that are modified by tobacco smoke exposure.

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