Published in final edited form as:
*Epidemiology*. 2001 September ; 12(5): 577–583.

# Family history and the risk of early onset persistent, early onset transient and late onset asthma

**Stephanie J. London**[1], **W. James Gauderman**[2], **Edward Avol**[2], **Edward B. Rappaport**[2], and **John M. Peters**[2]

1 *Epidemiology Branch, National Institute of Environmental Health Sciences*

2 *Department of Preventive Medicine, Keck School of Medicine, University of Southern California*

## Abstract

Family history of asthma and allergies strongly influences asthma risk in children but the association may differ for early onset persistent, early onset transient, and late onset asthma. We analyzed the relation between family history and these types of asthma using cross-sectional data from a school-based study of 5,046 Southern California children. Parental and/or sibling history of asthma and allergy were generally more strongly associated with early onset persistent asthma compared with early onset transient or late onset asthma. For children with two asthmatic parents relative to those with none, the prevalence ratio (PR) for early onset persistent asthma was 12.1 [95% confidence interval (CI) 7.91–18.7] compared with 7.51 (95% CI 2.62–21.5) for early onset transient asthma and 5.38 (95% CI 3.40–8.50) for late onset asthma. Maternal smoking in pregnancy was predominantly related to the risk of early onset persistent asthma in the presence of parental history of allergy and asthma and the joint effects were more than additive (interaction contrast ratio = 3.10, 95% CI 1.45–4.75). Our results confirm earlier data that parental history of asthma and allergy is most strongly associated with early onset persistent asthma and suggest that among genetically predisposed children, an early life environmental exposure, maternal smoking during pregnancy, favors the development of early onset asthma that persists into later early childhood.

### Keywords

asthma; wheeze; genetic susceptibility; parental; smoking; pregnancy; in *utero*; sibling

## Introduction

Many studies have shown that family history of asthma and allergy increases the risk of asthma in children.[1] Based on data from a prospective birth cohort, Martinez *et al*. have proposed that parental history of asthma and allergy relates most strongly to early onset asthma that persists into later childhood, as opposed to early onset transient or late onset asthma.[2,3] Few data have been presented by these different categories of asthma. Rusconi *et al*.[4] recently reported, in cross-sectional data from Italy, that parental history of asthma was most strongly associated with early onset persistent wheezing.

Correspondence to: Dr. Stephanie London, NIEHS, PO Box 12233, MD A3-05, RTP NC 27709. Telephone 919-541-5772, fax 919-541-2511..

This work was supported in part by the California Air Resources Board (Contract A033-186), the National Institute of Environmental Health Sciences (Grants 1PO1ESO939581-05, #5P30ES07048-02, and RO1ES10421 as well as Division of Intramural Research Project Z01 ES49019), the Environmental Protection Agency (Grant #R826708-01-0), the National Heart, Lung and Blood Institute (Grant #R01 HL/ES61768-01) and the Hastings Foundation.

If parental history of asthma and allergy leads preferentially to early onset persistent asthma, this has ramifications for studying early life environmental factors, because genetics and environment appear to interact in asthma etiology.[5] We postulated that a relevant early life exposure, maternal smoking during pregnancy, might lead to early onset persistent asthma among the genetically predisposed.

We examined the association between family history of asthma and allergy and risk of early onset persistent, early onset transient and late onset asthma using cross-sectional data from the Children's Health Study, a school-based study of children aged 9–16 residing in 12 Southern California communities and enrolled between 1993 and 1996. We also examined whether parental history might influence the association between maternal smoking during pregnancy and the three classes of asthma -- early onset persistent, early onset transient and late onset asthma.

## Methods

Details of the baseline enrollment have been previously published.[6] In brief, we designed the Children's Health Study to examine health effects of long term exposure to the air pollution mix in Southern California. We chose twelve Southern California communities based on historical measurements of air quality, demographic factors and a cooperative school district. In the spring of 1993, we enrolled the initial group of 3,681 students comprising approximately 50% fourth graders (age 9–10 years), 25% seventh graders (age 12–13 years) and 25% tenth graders (age 15–16 years) in public schools. We enrolled an additional 497 children in the fifth (age 10–11 years) and eighth grades (age 13–14 years) during 1994 and 2,081 additional students in fourth grade classes during 1996 for a total of 6,259 children.

Parents or guardians completed a self-administered questionnaire during the school year of entry into the study. The questionnaire contained items on history of respiratory illness and symptoms, other medical history, residential history, smoking and other exposures in the home, and family history of asthma and allergy. Parents completed the instrument in English or Spanish depending on their preference.

For this analysis, we classified medically diagnosed asthma based on a "yes" response to the question " Has a doctor ever diagnosed this child as having asthma?" or by the response of "asthma" to questions on specific diagnoses of respiratory illnesses at different ages. Using these questionnaire responses, we classified the age of onset into early (up to and including age 3) and late (after age 3). We assigned children to "persistent" asthma if parents reported that the child had one or more episodes of asthma in the past 12 months, any wheezing in the past 12 months, medication use for asthma or wheezing in the past 12 months or emergency room visit or hospitalization for wheeze or asthma in the past 12 months. Based on age at diagnosis and persistence, we placed children into one of three groups based on the schema of Martinez *et al.*[2] -- early onset persistent, early onset transient and late onset asthma.

We assigned children to the category of "wheeze or asthma-like illness without diagnosis of asthma" if their parents responded with "yes" to at least one of the above items on asthma episodes or asthma medication use but did not report a doctor's diagnosis of asthma. This category also included children whose parents did not report a doctor's diagnosis of asthma but gave a "yes" response to one of 11 questions regarding whether a child had ever had wheezing with or without colds, exercise, or shortness of breath, or whether the child had ever had nocturnal awakening due to wheezing or had ever required medical attention or treatment for wheezing. Because we asked about age at onset only for children whose parents reported a doctor diagnosis of asthma, we could not further classify children in the category of "wheeze or asthma-like illness without diagnosis of asthma" by age at onset.

Children who did not meet the above criteria for "medically diagnosed asthma" or "wheeze or asthma-like illness without asthma diagnosis" were classified as having "no wheeze or asthma". We excluded subjects who could not be classified into any of the five categories due to missing or "don't know" responses (134 subjects).

To minimize misclassification of parental history of asthma and allergy, we restricted the analysis to subjects for whom a biologic parent completed the questionnaire, resulting in the deletion of 483 subjects from the total study population. Maternal history of asthma was determined by response to the question "Has a doctor ever said that your child's biologic mother had asthma?". We determined maternal history of allergies by response to the question "Has a doctor ever said that your child's biologic mother had hay fever or allergies?". Responses to identical questions referring to the child's biologic father determined paternal history of asthma and allergies. We excluded subjects with missing or "don't know" responses to any of these four parental history questions (596 subjects) leaving 5,046 children for analyses of parental history in relation to asthma.

We classified the 3,921 children who reported having one or more full siblings, as having a sibling history of asthma if they reported one or more siblings in response to the question "How many – if any – of these brothers and sisters have been told by a doctor that they have asthma?". We classified sibling history of allergies by a response of one or more siblings to a parallel question on "hay fever or allergies".

We considered subjects exposed to maternal smoking during pregnancy based on a "yes" response to the question "Did your child's biologic mother smoke while she was pregnant with your child? - Include time when she was pregnant but did not yet know that she was.". For analyses of this variable, the dataset is reduced to 5022 subjects. A "yes" response to the question "Does anyone living in this child's home currently smoke cigarettes, cigars or pipes on a daily basis inside the home?" constituted current smoking in the home. Subjects responding "yes" were also asked "Who smoked inside this child's home on a daily basis?" with the choices of "mother", "father" and "other". We ascertained past smoking with an analogous pair of questions about past daily smoking in the home.

## Statistical analysis

We calculated prevalences separately for each of the four outcomes – early onset persistent asthma, early onset transient asthma, late onset asthma and "wheeze and asthma-like illness without doctor diagnosis" – in combination with the common comparison group of "No wheeze or asthma". We calculated prevalence ratios and their 95% confidence intervals using Proc Genmod in SAS (Version 8.1).

We evaluated possible confounding by design variables (community of residence or year of entry into the study) and by known and suspected risk factors for asthma obtained on our questionnaire. These included age, sex, race, parental income and education, dogs or cats in the home, household vermin, houseplants, water damage in the home, mold or mildew in the home, gas stove use, air conditioner use, number of siblings, maternal smoking in pregnancy, daily current smoking in the home, past daily smoking in the home, and medical insurance coverage for the child. Due to nonconvergence in multivariate models for the sparsest outcome category of early onset transient asthma in Proc Genmod, we assessed confounding on the odds ratio scale using logistic regression (Proc Catmod in SAS Version 8.1) among the 4,210 out of 5,046 subjects with nonmissing data on all potential confounders. Because the family history variables were strongly associated with the outcomes but not appreciably associated with these potential confounders, which were less strongly associated with the outcomes, adjustment for

these variables, either singly or in combination, did not appreciably alter the crude prevalence ratios. Therefore, we present only the unadjusted prevalence ratios.

To assess confounding of association with maternal smoking during pregnancy, we evaluated the effect of adjustment for terms for past daily smoking in the home and current daily smoking in the home. Inclusion of these two terms or six separate terms for past or current smoking by mother, father and other persons did not measurably alter the crude results for maternal smoking during pregnancy. Thus we present prevalence ratios for maternal smoking in pregnancy from models including only the other term in Table 3 -- parental history of asthma or allergy.

To assess the additivity of joint effects of maternal smoking in pregnancy and parent history of asthma and allergy, we calculated the interaction contrast ratio (previously referred to as the "relative excess risk for interaction") and its 95% confidence interval from the prevalence ratios using the method of Hosmer and Lemeshow[9]. We calculated the interaction contrasts and 95% confidence intervals from the prevalence rates as described by Rothman and Greenland [8]. The interaction contrast and interaction contrast ratio take on the value of zero when the joint effects of two factors are simply additive[8].

## Results

Among the 5,046 subjects, 729 (14 %) had a parental report of doctor-diagnosed asthma. Among these 729 children with asthma diagnosis, we classified 219 as having early onset persistent, 106 as having early onset transient asthma, and 404 as having late onset asthma. We classified 950 subjects (19 %) into the category of "wheeze or asthma-like illness without asthma diagnosis". The remaining 3367 (67 %) comprised the common comparison group of "no wheeze or asthma".

Parental asthma was strongly associated with the prevalence of doctor-diagnosed asthma of all three types (Table 1). Early onset persistent asthma generally associated more strongly with parental history of asthma than either early onset transient or late onset asthma (Table 1). Subjects with two asthmatic parents, relative to those with none, had a prevalence ratio for early onset persistent asthma of 12.1 (95% CI 7.91–18.7) compared with 7.51 (95% CI 2.62–21.5) for early onset transient and 5.38 (95% CI 3.40–8.50) for late onset asthma.

Parental history of allergy associated with childhood asthma less strongly than parental asthma (Table 1). Parental history of allergy associated most strongly with early onset persistent asthma and least strongly with early onset transient asthma. For subjects with two allergic parents relative to none, we found prevalence ratios of 5.11 (95% CI 3.68–7.12) for early onset persistent asthma compared with 1.83 (95% CI 0.98–3.41) for early onset transient asthma and 3.50 (95% CI 2.68–4.57) for late onset asthma (Table 1).

Maternal and paternal histories of asthma related about equally with asthma outcomes in the child (Table 1). Paternal history of asthma was slightly more strongly associated with early onset transient asthma than maternal history but small numbers in this outcome category limit precision. The associations between parental allergy and the child's asthma also differed little according to which parent was affected.

To assess the risk of asthma in children according to parental history of asthma and allergy together, we created an index based on Litonjua *et al* [7] (Table 1). Relative to children with no parental history of asthma or allergy, we observed a stronger association with early onset persistent asthma than with either early onset transient asthma or late onset asthma for each level of the combined parental allergy and asthma variable. The only exception was for subjects with no asthmatic and one allergic parent where the prevalence ratios for early onset persistent and late onset asthma were essentially identical (2.01 versus 2.21 respectively). For each

outcome, having a parent with asthma and atopy conferred a stronger association than having only one parent with asthma or allergy alone (Table 1).

Among subjects reported to have a full sibling, we created mutually exclusive categories combining parent and sibling histories to assess the independent contribution of sibling history of asthma and allergy (Table 2). Sibling history of asthma strongly associated with all three types of asthma even in the absence of parental asthma. As with parental history alone, we generally found the strongest associations between sibling history and early onset persistent asthma. Adjustment for number of siblings, which was inversely associated with all outcomes (data not shown), did not appreciably alter the associations between the various outcomes and sibling history of asthma or allergy.

Maternal smoking during pregnancy was moderately associated with both types of early onset asthma and with wheeze and was least strongly associated with late onset asthma (Table 3). We considered whether parental history of allergy or asthma might modify the association between maternal smoking during pregnancy and specific types of asthma. In stratified analyses, among children with a parental history of asthma or allergy, maternal smoking in pregnancy appeared to relate most strongly to early onset persistent asthma. In contrast, among children with no parental history, maternal smoking in pregnancy associated predominantly with the other three types, particularly early onset transient asthma and wheeze.

To assess effect-measure modification on the additive scale, we created dummy variables for the four combinations of parental history of asthma or allergy and maternal smoking in pregnancy (Table 3). For early onset persistent asthma, we found evidence that the joint effect of maternal smoking in pregnancy and family history of asthma and allergy was more than additive. Maternal smoking alone did not increase risk. For subjects with both maternal smoking in pregnancy and a parental history of allergy and asthma the observed prevalence ratio was 6.16 (95% CI 4.18–9.07) compared with a predicted prevalence ratio of 3.05 for additive joint effects. The interaction contrast ratio was 3.10 (95% CI 1.45–4.75) and the interaction contrast was 0.087 (95 % CI 0.035–0.139). For the other three outcomes, the joint effects of maternal smoking in pregnancy and parental history of asthma and allergy did not appreciably depart from additivity (Table 3).

## Discussion

Numerous studies have shown a strong association of asthma risk in children with family history of asthma and allergies.[10] However, few data relate family history to the asthma subtypes of early onset transient, early onset persistent and late onset asthma which appear to have different associations with various risk factors.[2,4] Consistent with reports by Martinez *et al.*[2] and Rusconi *et al*.[4], we found a stronger association between parental history of asthma and early onset persistent asthma as opposed to early onset transient asthma or late onset asthma. Parental history of allergy, particularly having two affected parents, also related most strongly with the risk of early onset persistent asthma. As in previous studies [1,4,7], we observed greater associations between childhood asthma risk and family history of asthma than family history of allergy.

We found that sibling history of asthma, even in the absence of parental history, was strongly associated with asthma and, as with parental history, the association was strongest with early onset persistent asthma. A strong and independent contribution of sibling history of asthma and allergy, beyond the contribution of parental history, could be consistent with shared early life environmental factors or the interaction of genetics and the early environment.

To evaluate the possibility that genetic susceptibility, approximated by parental history of asthma and allergy, modulates the association between very early life exposures and the various asthma types, we examined maternal smoking during pregnancy.

Maternal smoking in pregnancy was mildly associated with wheezing and all three asthma types. However, among those with parental history of asthma or allergy, maternal smoking in pregnancy predominantly associated with early onset asthma that persists into later childhood. The joint effects of maternal smoking in pregnancy and parental history of asthma and allergy in relation to early onset persistent asthma were more than additive, suggestive of a possible biologic interaction.

Although it is difficult to distinguish the independent effects of prenatal and postnatal maternal smoking, early exposure to a mother who smokes clearly increases the risk of wheezy illness and asthma in children, [11] and increasing evidence implicates prenatal maternal smoking *per se*.[12,13] Maternal smoking during pregnancy correlates with reduced lung function in newborns, measured prior to hospital discharge, who have not yet been exposed to postnatal smoking [14–16][15–17]. Maternal smoking in pregnancy has also been associated with pulmonary function decrements in school-aged children in this [18] and other studies. [19]

A biologic interaction between maternal smoking in pregnancy and family history of asthma and allergy is plausible. Asthma is a chronic inflammatory disorder of the airways and airway inflammation is related to the immune response[20]. The development of asthma in young children relates to the persistence of the Th-2 immune responses that characterize normal pregnancy [21]. Increasing evidence points to the influence of the *in utero* environment on the developing fetal immune response [21]. T-cell priming commonly occurs transplacentally to antigens encountered by the mother in the last trimester of pregnancy; with Th-2 skewing of these primed T-cells [21]. In mice, cigarette smoke promotes release of Th-2 cytokines after antigen challenge[22]. Smoking also primes human neutrophils leading to an enhanced inflammatory response to activators and production of tobacco anti-idiotypic antibodies that can continue this priming after smoking cessation [23]. Antibodies of this type could cross the placenta and stimulate fetal antibody formation [24]. In addition, during the third trimester, cigarette smoking blocks the decrease in circulating numbers of mature T-cells, particularly helper T-cells, seen in nonsmokers [24]. Infants with a family history of atopy and asthma have reduced production of interferon gamma, a Th-1 cytokine [21]. It is possible that in the infant with a genetic predisposition to asthma and allergy, the influence of maternal smoking on the subsequent development of immune responses favoring asthma could be heightened.

We are not aware of other data addressing the possible interaction of maternal smoking during pregnancy and parental history of asthma or allergy in relation to childhood asthma. Agabati *et al.* [12] reported that current maternal smoking was related to current asthma among children aged 6–7 in the presence of parental asthma history, but only to wheeze in the absence of parental history.

Like many epidemiologic studies of childhood asthma, ours has several weaknesses. We classified children as asthmatic based on parental report of a doctor's diagnosis rather than on objective measures of bronchial responsiveness. Misclassification of asthma would most likely bias results toward the null if nondifferential with respect to family history. In addition, the findings of Martinez *et al*.[2] and Rusconi *et al*.[4] were based on report of wheeze rather than asthma diagnosis. Unfortunately, we lacked data on the age of onset of wheezing for children without a reported doctor diagnosis of asthma. Early onset transient wheezing is reported to be very common; [2] whereas in our data early onset transient asthma was not. Classifying a large number of early transient wheezers into our category of wheeze and asthma-like illness without asthma diagnosis limits our power to study early transient illness. Further,

ascertainment of a history of transient wheezing in early life among older children will likely result in misclassification of some early transient wheezers into the comparison group. Parents may not consistently report the symptoms of children whose wheezing resolved long ago. If this underreporting does not depend on family history, it would probably bias results toward the null.

The cross-sectional nature of these data also poses the danger of differential misclassification. We ascertained parental history of asthma simultaneously with report of asthma in the child. Thus, the pattern of associations seen in our study, as well as in the study of Rusconi *et al.* [4], could result from biased parental reporting of childhood asthma or wheeze contingent on family history, or, conversely, from child's asthma or wheeze influencing reporting of family history. Kulig *et al*. [25], using prospective birth cohort data, found that fathers' reports of their atopic histories changed after their infants developed atopic dermatitis. This same distortion occurred when mothers provided the father's history of atopy. However, the data of Kulig *et al*. [25] provide reassurance in that the child's development of atopic disease did not influence the mother's report of her atopic history. Further, distortion in reporting of paternal history did not occur when the infant had developed atopic manifestations other than atopic dermatitis [25]. We cannot evaluate the possibility of recall bias in parental responses directly in our cross-sectional data. To decrease both differential and nondifferential misclassification, we restricted the analysis to subjects for whom a biologic parent completed the questionnaire. Because we based our assessment of parental history on the report of one parent, generally the mother, we examined whether the results were similar for questionnaires completed by mothers and fathers and found that they were.

We did not find stronger associations between childhood asthma and history of asthma in the mother versus the father. Stronger associations for maternal history have been inconsistently observed in the literature [26]. Recent data suggests that differences in risk conferred by maternal versus paternal history might depend on the specific allergen to which the asthmatic child responds [27].

In summary, in this school-based study of Southern California children, we found that family history of asthma and allergy associated most strongly with the risk of early onset persistent asthma. We also found preliminary evidence that parental history of asthma and allergy may influence whether an early environmental exposure, maternal smoking during pregnancy, results in early onset asthma that persists into later childhood. If confirmed, these results may be relevant to the study of early life environmental exposures, such as air pollution, for which associations with asthma have been postulated but have been difficult to detect [28]. Other early life exposures may be differentially related to childhood asthma depending on age at onset and persistence of asthma and these relations may differ according to genetic predisposition.

**Acknowledgements**

The statements and conclusions in this report are those of the investigators and not necessarily those of the California Air Resources Board, the Environmental Protection Agency, or the National Institute of Environmental Health Sciences. The mention of commercial products, their source, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products.

We thank Ms. Marsha Shepherd and Dr. David Shore of Westat, Inc (Research Triangle Park, NC) for expert programming and Jane Schroeder and David Umbach for helpful comments on the manuscript.

## References

1. Duffy DL. Genetic epidemiology of asthma. Epidemiol Rev 1997;19(1):129–43. [PubMed: 9360910]

2. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133–8. [PubMed: 7800004]
3. Martinez FD, Helms PJ. Types of asthma and wheezing. Eur Respir J Suppl 1998;27:3s–8s. [PubMed: 9699776]
4. Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, Renzoni E. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. Am J Respir Crit Care Med 1999;160(5 Pt 1):1617–22. [PubMed: 10556130]
5. Weiss ST. Gene by environment interaction and asthma. Clin Exp Allergy 1999;29 (Suppl 2):96–9. [PubMed: 10421831]
6. Peters JM, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, Linn WS, Margolis H, Rappaport E, Gong H, Thomas DC. A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. Am J Respir Crit Care Med 1999;159(3):760–7. [PubMed: 10051248]
7. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? Am J Respir Crit Care Med 1998;158(1):176–81. [PubMed: 9655726]
8. Rothman, KJ.; Greenland, S. Philadelphia: Lippincott Williams and Wilkins; 1998. Modern Epidemiology.
9. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. Epidemiology 1992;3(5): 452–6. [PubMed: 1391139]
10. Sandford AJ, Pare PD. The genetics of asthma. The important questions. Am J Respir Crit Care Med 2000;161(3 Pt 2):S202–6. [PubMed: 10712375]
11. Cook DG, Strachan DP. Health effects of passive smoking-10: Summary of effects of parental smoking on the respiratory health of children and implications for research. Thorax 1999;54(4):357–66. [PubMed: 10092699]
12. Agabiti N, Mallone S, Forastiere F, Corbo GM, Ferro S, Renzoni E, Sestini P, Rusconi F, Ciccone G, Viegi G, Chellini E, Piffer S. The impact of parental smoking on asthma and wheezing. SIDRIA Collaborative Group. Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente Epidemiology 1999;10(6):692–8.
13. Stein RT, Holberg CJ, Sherrill D, Wright AL, Morgan WJ, Taussig L, Martinez FD. Influence of parental smoking on respiratory symptoms during the first decade of life: the Tucson Children's Respiratory Study. Am J Epidemiol 1999;149(11):1030–7. [PubMed: 10355379]
14. Hoo AF, Henschen M, Dezateux C, Costeloe K, Stocks J. Respiratory function among preterm infants whose mothers smoked during pregnancy [see comments]. Am J Respir Crit Care Med 1998;158(3): 700–5. [PubMed: 9730993]
15. Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. Eur Respir J 1997;10(8):1774–9. [PubMed: 9272918]
16. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouef PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 1996;348(9034): 1060–4. [PubMed: 8874457]
17. Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, Weiss ST, Speizer FE. The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis 1992;145(5):1129–35. [PubMed: 1586058]
18. Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, Avol E, Peters JM. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. Thorax 2000;55(4):271–6. [PubMed: 10722765]
19. Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. Am J Epidemiol 1994;139(12):1139–52. [PubMed: 8209873]
20. Cookson WO, Moffatt MF. Asthma: an epidemic in the absence of infection? [comment]. Science 1997;275(5296):41–2. [PubMed: 8999535]
21. Holt PG, Macaubas C, Prescott SL, Sly PD. Primary sensitization to inhalant allergens [In Process Citation]. Am J Respir Crit Care Med 2000;162(3 Pt 2):S91–4. [PubMed: 10988159]

22. Seymour BW, Pinkerton KE, Friebertshauser KE, Coffman RL, Gershwin LJ. Second-hand smoke is an adjuvant for T helper-2 responses in a murine model of allergy. J Immunol 1997;159(12):6169–75. [PubMed: 9550419]

23. Koethe SM, Kuhnmuench JR, Becker CG. Neutrophil priming by cigarette smoke condensate and a tobacco anti- idiotypic antibody [In Process Citation]. Am J Pathol 2000;157(5):1735–43. [PubMed: 11073832]

24. Bjorksten, B.; Kjellman, N-I.; Zeiger, RS. Development and prevention of allergic disease in childhood. In: Middleton, E.; Ellis, EF.; Yunginger, JW.; Reed, CE.; Adkinson, NF.; Busse, WW., editors. Allergy: Principle and Practice. Vol 2. St. Louis: Mosby; 1998. p. 816-837.

25. Kulig M, Bergmann R, Edenharter G, Wahn U. Does allergy in parents depend on allergy in their children? Recall bias in parental questioning of atopic diseases. Multicenter Allergy Study Group. J Allergy Clin Immunol 2000;105(2 Pt 1):274–8. [PubMed: 10669847]

26. Cogswell JJ. Influence of maternal atopy on atopy in the offspring. Clin Exp Allergy 2000;30(1):1–3. [PubMed: 10606923]

27. Halonen M, Stern DA, Lohman C, Wright AL, Brown MA, Martinez FD. Two subphenotypes of childhood asthma that differ in maternal and paternal influences on asthma risk. Am J Respir Crit Care Med 1999;160(2):564–70. [PubMed: 10430729]

28. Burney P. Air pollution and asthma: the dog that doesn't always bark. Lancet 1999;353(9156):859–60. [PubMed: 10093974]

**Table 1**

Parental history of asthma and allergies and personal history of atopy in relation to childhood asthma

| Variable | No asthma or wheeze | Early onset persistent asthma | | | Early onset transient asthma | | | Late onset asthma | | | Wheeze and asthma-like illness w/o asthma diagnosis | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | N | Prev * | PR (95% CI) + | N | Prev | PR (95% CI) | N | Prev | PR (95% CI) | N | Prev | PR (95% CI) |
| Parental asthma | | | | | | | | | | | | | |
| none | 2907 | 120 | 0.040 | 1.00 | 70 | 0.024 | 1.00 | 259 | 0.082 | 1.00 | 741 | 0.203 | 1.00 |
| mother | 250 | 48 | 0.161 | 4.06 (2.97 – 5.56) | 14 | 0.053 | 2.26 (1.29 – 3.95) | 78 | 0.238 | 2.91 (2.32 – 3.65) | 127 | 0.337 | 1.66 (1.42 – 1.94) |
| father | 196 | 38 | 0.162 | 4.10 (2.92 – 5.75) | 19 | 0.088 | 3.76 (2.31 – 6.12) | 56 | 0.222 | 2.72 (2.10 – 3.52) | 70 | 0.263 | 1.30 (1.05 – 1.60) |
| both | 14 | 13 | 0.481 | 12.1 (7.91 – 18.7) | 3 | 0.176 | 7.51 (2.62 – 21.5) | 11 | 0.440 | 5.38 (3.40 – 8.50) | 12 | 0.462 | 2.27 (1.49 – 3.46) |
| Parental allergy | | | | | | | | | | | | | |
| none | 2028 | 70 | 0.033 | 1.00 | 47 | 0.023 | 1.00 | 127 | 0.059 | 1.00 | 438 | 0.178 | 1.00 |
| mother | 613 | 48 | 0.073 | 2.18 (1.52 – 3.11) | 24 | 0.038 | 1.66 (1.03 – 2.70) | 120 | 0.164 | 2.78 (2.20 – 3.51) | 230 | 0.273 | 1.54 (1.34 – 1.77) |
| father | 449 | 44 | 0.089 | 2.67 (1.86 – 3.85) | 23 | 0.049 | 2.15 (1.32 – 3.51) | 85 | 0.159 | 2.70 (2.09 – 3.50) | 147 | 0.247 | 1.39 (1.18 – 1.64) |
| both | 277 | 57 | 0.171 | 5.11 (3.68 – 7.12) | 12 | 0.042 | 1.83 (0.98 – 3.41) | 72 | 0.206 | 3.50 (2.68 – 4.57) | 135 | 0.328 | 1.84 (1.57 – 2.17) |
| Parental allergy and asthma combined | | | | | | | | | | | | | |
| none | 1920 | 54 | 0.027 | 1.00 | 39 | 0.020 | 1.00 | 116 | 0.057 | 1.00 | 396 | 0.171 | 1.00 |
| 0 asthmatic, 1 allergic | 791 | 46 | 0.055 | 2.01 (1.37 – 2.95) | 26 | 0.032 | 1.60 (0.98 – 2.61) | 114 | 0.126 | 2.21 (1.73 – 2.83) | 261 | 0.248 | 1.45 (1.26 – 1.67) |
| 0 asthmatic, 2 allergic | 196 | 20 | 0.093 | 3.38 (2.07 – 5.54) | 5 | 0.025 | 1.25 (0.50 – 3.13) | 29 | 0.129 | 2.26 (1.54 – 3.32) | 84 | 0.300 | 1.75 (1.44 – 2.14) |
| 1 asthmatic, 0 allergic | 349 | 54 | 0.134 | 4.90 (3.41 – 7.03) | 25 | 0.067 | 3.36 (2.06 – 5.48) | 97 | 0.217 | 3.82 (2.98 – 4.90) | 140 | 0.286 | 1.67 (1.42 – 1.98) |
| 1 asthmatic, 1 allergic | 97 | 32 | 0.248 | 9.07 (6.08 – 13.5) | 8 | 0.076 | 3.83 (1.84 – 7.98) | 37 | 0.276 | 4.85 (3.50 – 6.72) | 57 | 0.370 | 2.16 (1.73 – 2.71) |
| 2 asthmatic | 14 | 13 | 0.481 | 17.6 (11.0 – 28.2) | 3 | 0.176 | 8.86 (3.03 – 25.9) | 11 | 0.440 | 7.72 (4.80 – 12.0) | 12 | 0.462 | 2.70 (1.77 – 4.13) |

* Prevalence, computed for each outcome separately with the common comparison group of "No asthma or wheeze".

+ Prevalence ratio and 95% confidence intervals.

**Table 2**

Odds ratios for asthma according to sibling and parental history of asthma and allergy among children with a sibling

| Variable | No wheeze or asthma | Early onset persistent asthma | | | Early onset transient asthma | | | Late onset asthma | | | Wheeze and asthma-like illness w/ o asthma | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | N | Prev * | PR (95% CI) + | N | Prev | PR (95% CI) | N | Prev | (95% CI) | N | Prev | PR (95% CI) |
| Asthma present in: | | | | | | | | | | | | | |
| no parent or sibling | 1908 | 54 | 0.028 | 1.00 | 33 | 0.017 | 1.00 | 147 | 0.072 | 1.00 | 490 | 0.204 | 1.00 |
| no sibling, 1 parent | 248 | 29 | 0.105 | 3.80 (2.47 – 5.87 ) | 16 | 0.061 | 3.56 (1.99 – 6.39) | 61 | 0.197 | 2.76 (2.1 – 3.63 ) | 103 | 0.293 | 1.44 (1.20 – 1.72 ) |
| no sibling, 2 parents | 8 | 2 | 0.200 | 7.27 (2.05 – 25.8 ) | 2 | 0.200 | 11.8 (3.25 – 42.5) | 5 | 0.385 | 5.38 (2.66 – 10.9 ) | 4 | 0.333 | 1.63 (0.73 – 3.65 ) |
| 1+ sibling, no parent | 307 | 45 | 0.128 | 4.64 (3.18 – 6.79 ) | 20 | 0.061 | 3.60 (2.09 – 6.19) | 62 | 0.168 | 2.35 (1.78 – 3.09 ) | 77 | 0.201 | 0.98 (0.79 – 1.22 ) |
| 1+ sibling, 1 parent | 121 | 42 | 0.258 | 9.36 (6.47 – 13.6 ) | 9 | 0.069 | 4.07 (1.99 – 8.33) | 46 | 0.275 | 3.85 (2.88 – 5.15 ) | 60 | 0.331 | 1.62 (1.30 – 2.02 ) |
| 1+ sibling, 2 parents | 4 | 6 | 0.600 | 21.8 (12.3 – 38.6 ) | 1 | 0.200 | 11.8 (1.97 – 70.1) | 5 | 0.556 | 7.77 (4.24 – 14.2 ) | 6 | 0.600 | 2.94 (1.76 – 4.90 ) |
| Allergy present in: | | | | | | | | | | | | | |
| no parent or sibling | 1252 | 51 | 0.039 | 1.00 | 25 | 0.020 | 1.00 | 75 | 0.057 | 1.00 | 243 | 0.163 | 1.00 |
| no sibling, 1 parent | 516 | 42 | 0.075 | 1.92 (1.29 – 2.86 ) | 24 | 0.044 | 2.27 (1.31 – 3.94 ) | 90 | 0.149 | 2.63 (1.96 – 3.52 ) | 176 | 0.254 | 1.56 (1.32 – 1.86 ) |
| no sibling, 2 parents | 96 | 10 | 0.094 | 2.41 (1.26 – 4.61 ) | 2 | 0.020 | 1.04 (0.25 – 4.34 ) | 18 | 0.158 | 2.79 (1.73 – 4.5 ) | 34 | 0.262 | 1.61 (1.18 – 2.2 ) |
| 1+ sibling, no parent | 227 | 7 | 0.030 | 0.76 (0.35 – 1.66 ) | 4 | 0.017 | 0.88 (0.31 – 2.52 ) | 26 | 0.103 | 1.82 (1.19 – 2.78 ) | 74 | 0.246 | 1.51 (1.20 – 1.9 ) |
| 1+ sibling, 1 parent | 374 | 33 | 0.081 | 2.07 (1.36 – 3.16 ) | 17 | 0.043 | 2.22 (1.21 – 4.07 ) | 77 | 0.171 | 3.02 (2.24 – 4.08 ) | 133 | 0.262 | 1.61 (1.34 – 1.94 ) |
| 1+ sibling, 2 parents | 131 | 35 | 0.211 | 5.39 (3.62 – 8.03 ) | 9 | 0.064 | 3.28 (1.56 – 6.89 ) | 40 | 0.234 | 4.14 (2.92 – 5.87 ) | 80 | 0.379 | 2.33 (1.90 – 2.87 ) |

* Prevalence, computed for each outcome separately with the common comparison group of "No asthma or wheeze"

+ Prevalence ratio and 95% confidence intervals.

**Table 3**

Maternal smoking in relation to early onset transient, early onset persistent, and late onset asthma according to parental history of asthma and allergy

| | No asthma or wheeze | Early onset persistent asthma | | | Early onset transient asthma | | | Late onset asthma | | | Wheeze or asthma-like illness without MD Diagnosis | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | N | Prev * | PR (95% CI) + | N | Prev | PR (95% CI) | N | Prev | PR (95% CI) | N | Prev | PR (95% CI) |
| All subjects, regardless of family history: Maternal smoking during pregnancy | | | | | | | | | | | | | |
| No | 2858 | 166 | 0.055 | 1.00 | 81 | 0.028 | 1.00 | 330 | 0.104 | 1.00 | 724 | 0.202 | 1.00 |
| Yes | 488 | 52 | 0.096 | 1.70 (1.27 – 2.27) | 25 | 0.049 | 1.74 (1.13 – 2.70) | 74 | 0.132 | 1.24 (0.99 – 1.57) | 224 | 0.315 | 1.53 (1.350 – 1.73) |
| Parental History of Allergy or Asthma | | | | | | | | | | | | | |
| No | 1904 | 54 | 0.028 | 1.00 | 39 | 0.020 | 1.00 | 116 | 0.057 | 1.00 | 395 | 0.172 | 1.00 |
| Yes | 1442 | 164 | 0.102 | 3.67 (2.72 – 4.95) | 67 | 0.044 | 2.20 (1.49 – 3.24) | 288 | 0.166 | 2.89 (2.35 – 3.55) | 553 | 0.277 | 1.60 (1.430 – 1.79) |
| Parental family history or asthma or allergy=No: Maternal smoking in pregnancy | | | | | | | | | | | | | |
| No | 1632 | 47 | 0.028 | 1.00 | 27 | 0.016 | 1.00 | 90 | 0.052 | 1.00 | 283 | 0.148 | 1.00 |
| Yes | 272 | 7 | 0.025 | 0.90 (0.41 – 1.96) | 12 | 0.042 | 2.59 (1.33 – 5.07) | 26 | 0.087 | 1.67 (1.10 – 2.54) | 112 | 0.292 | 1.97 (1.630 – 2.39) |
| Parental family history or asthma or allergy=Yes: Maternal smoking in pregnancy | | | | | | | | | | | | | |
| No | 1226 | 119 | 0.088 | 1.00 | 54 | 0.042 | 1.00 | 240 | 0.164 | 1.00 | 441 | 0.265 | 1.00 |
| Yes | 216 | 45 | 0.172 | 1.95 (1.42 – 2.67) | 13 | 0.057 | 1.35 (0.75 – 2.43) | 48 | 0.182 | 1.11 (0.84 – 1.47) | 112 | 0.341 | 1.29 (1.090 – 1.53) |
| Maternal smoking during pregnancy and parental history of asthma or allergy combined: | | | | | | | | | | | | | |
| Neither | 1632 | 47 | 0.028 | 1.00 | 27 | 0.016 | 1.00 | 90 | 0.052 | 1.00 | 283 | 0.148 | 1.00 |
| Smoking only | 272 | 7 | 0.025 | 0.90 (0.41 – 1.96) | 12 | 0.042 | 2.60 (1.33 – 5.07) | 26 | 0.087 | 1.67 (1.10 – 2.54) | 112 | 0.292 | 1.97 (1.633 – 2.39) |
| Parental history only | 1226 | 119 | 0.088 | 3.16 (2.27 – 4.40) | 54 | 0.042 | 2.59 (1.64 – 4.09) | 240 | 0.164 | 3.13 (2.48 – 3.95) | 441 | 0.265 | 1.79 (1.566 – 2.05) |
| Joint | 216 | 45 | 0.172 | 6.16 (4.18 – 9.07) | 13 | 0.057 | 3.49 (1.83 – 6.66) | 48 | 0.182 | 3.48 (2.51 – 4.82) | 112 | 0.341 | 2.31 (1.921 – 2.78) |
| Joint, predicted under additive model | | | | 3.05 | | | 4.19 | | | 3.80 | | | 2.76 |
| Interaction contrast ratio (95% CI) ++ | | | | 3.10 (1.45 – 4.75) | | | −0.70 (−3.21 – 1.81) | | | −0.32 (−1.49 – 0.85) | | | −0.45 ( −0.963 – 0.06) |
| Interaction contrast (95% CI) | | | | 0.087 (0.035 – 0.139) | | | −0.011 (−80.5 – 80.1) | | | −0.017 (−80.5 – 80.1) | | | −0.067 ( −0.141 – 0.006) |

* Prevalence, computed for each outcome separately with the common comparison group of "No asthma or wheeze". Analyses exclude 24 subjects missing information on maternal smoking during pregnancy.

+ Prevalence ratios and 95% confidence intervals. Prevalence ratios for maternal smoking in pregnancy and parental history of allergy and asthma are mutually adjusted. Other prevalence ratios in table are unadjusted.

++ The interaction contrast ratio and the interaction contrast have the value of zero when the joint effects are simply additive.