Gene–environment interactions in the study of asthma in the postgenomewide association studies era

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Purpose of review
Asthma is a complex disease characterized by an intricate interplay of both heritable and environmental factors. Understanding the mechanisms through which genes and environment interact represents one of the major challenges for pulmonary researchers. This review provides an overview of the recently published literature on gene–environment (G × E) interactions in asthma, with a special focus on the new methodological developments in the postgenomewide association studies (GWAS) era.

Recent findings
Most recent studies on G × E interaction in asthma used a candidate-gene approach. Candidate-gene studies considering exposure to outdoor air pollutants showed significant interactions mainly with variants in the *GSTP1* gene on asthma in children. G × E studies on passive and active smoking, including one genomewide interaction study, identified novel genes of susceptibility to asthma and a time-dependent effect of maternal smoking. Other recent studies on asthma found interactions between candidate genes and occupational allergen exposure and several domestic exposures such as endotoxin and gas cooking. New methods were developed to efficiently estimate G × E interaction in GWAS, and a pathway-based strategy to select an enriched gene-set for G × E studies has recently been proposed.

Summary
The G × E studies presented in this review offer a good example on how candidate-gene approaches can complement and help in validating GWAS findings.

Keywords
asthma, environmental exposure, gene–environment interaction, genomewide association studies

INTRODUCTION

It is now well established that heritable and environmental factors play a role in asthma pathogenesis. Genetic factors are likely to be involved in the development, the activity and the severity of asthma, and they act primarily through the complex mechanisms that involve interactions with environmental factors and with other genes. Gene–environment (G × E) interaction studies aim to explain how the strength and direction of the associations between certain genetic variants and asthma may depend on the given environmental exposures, and vice versa. So far, most G × E interactions have been identified through hypothesis-driven research involving only few candidate genes (reviewed in [1]). To go further, investigating G × E interactions may help to better understand the role of the genes identified by genomewide association studies (GWAS) of asthma. For example, variants at chromosome 17q21 that emerged from GWAS have shown particularly strong associations with asthma in children who had had wheezing illnesses or tobacco exposures in early life [2,3▪▪]. Understanding the mechanisms through which genes and environment interact represents one of the major challenges for pulmonary researchers.

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KEY POINTS

- Candidate gene–environment interaction studies on asthma may help to better understand the role of the genes identified by genomewide association studies.
- Variants in the *GSTP1* and *GSTM1* gene modify the association of exposure to traffic-related outdoor air pollution, tobacco smoke exposure, and gas cooking with asthma outcomes in children and adults.
- Gene–smoking interaction studies add further evidence that passive smoking during pregnancy and in childhood increases the risk of asthma, with an effect that varies with the intensity of exposure and time, and is more pronounced in children carrying genetic variants that increase susceptibility.

This review will provide an overview of the recently published literature (January 2013 to September 2014) on G × E interactions in asthma, with a special focus on new methodological developments in the post-GWAS era.

RECENT FINDINGS

Most recent studies on G × E interaction in asthma used a candidate-gene approach (see Table 1 [3▪▪,4▪▪,5,6▪,7▪,8▪▪,9▪,10–12,13▪▪,14–16,17▪▪, 18▪▪, 19▪,20▪▪,21▪,22▪]). Among the various environmental factors, outdoor air pollution and smoking were the most studied.

Outdoor air pollution exposure

High levels of outdoor air pollutants such as particulate matter, nitrogen dioxide (NO_2), and ozone (O_3) have been associated with a higher risk of asthma [23], mainly in children. Exposure to air pollution can cause oxidative stress, and it is plausible that genetic variants involved in inflammation and protection against reactive oxygen species (ROS) may influence the response to air pollutants. Several recent candidate-gene studies explored the interactive effect between ambient outdoor pollutants and genes in the Nuclear factor-like 2 (Nrf2) antioxidant response pathway. Genes in this pathway, such as those belonging to the glutathione S-transferase (GST) family [glutathione S-transferase mu 1 (*GSTM1*) and glutathione S-transferase pi 1 (*GSTP1*)] and *NAD(P)H* dehydrogenase quinone 1 (*NQO1*), are responsible for the expression of enzymes that conjugate and inactivate ROS. Interactive effects of variants in the *GSTP1* gene with fine particles ($PM_{2.5}$) and O_3 were observed on asthma and wheezing in children. Children carrying the rs1695 Ile105Val allele were at increased risk of asthma and wheezing associated with exposure to traffic-related NO_2 [4▪▪], $PM_{2.5}$ and O_3 [5], and at increased risk for asthma if they were exposed to outdoor inhalable coarse particles (PM_{10}) [6▪]. Interestingly, Su *et al.* [6▪] used multifactor dimensionality reduction (MDR) techniques to explore the interactions. The joint effect of rs1695 with O_3 was observed also on aeroallergen sensitization [7▪]. In addition, children carrying the minor allele for *GSTP1* rs11338272 were more susceptible to have asthma and wheezing when exposed to NO_2 compared with homozygous major allele carriers [4▪▪]. Suggestive evidence of an interaction between one single-nucleotide polymorphism (SNP; rs2234922) in the epoxide hydrolase 1 (*EPHX1*) gene and NO_2 was also found in children with asthma [6▪]. Variants involved in immune response, located in genes such as tumor necrosis factor alpha (*TNFA*) and Toll-like receptor 4 (*TLR4*), also seem to modify the association between exposure to outdoor air pollutants and asthma, as summarized recently by Vawda *et al.* [24▪▪].

Smoking exposure

During the last 18 months, the literature on interaction between genetic variants and smoking exposure provided new insights mostly into early-onset asthma considering parental or maternal smoking during pregnancy or early childhood, and into adult-onset asthma considering current and former smoking. Almost exclusively using a candidate approach, novel genes of susceptibility were suggested that are involved in inflammation, metabolism of xenobiotics, innate immunity, epithelial function, DNA methylation, or belonging to the 17q21 and 20p13 regions.

Only one genomewide study [8▪▪] of interaction (GEWIS) was conducted that involved 3048 asthmatic and 3509 nonasthmatic patients from studies participating in the GABRIEL Consortium (a multidisciplinary study to identify the genetic and environmental causes of asthma in the European community). Results from this study suggested the involvement of two novel genes of susceptibility to childhood asthma (age of onset <16 years). In particular, it showed suggestive evidence of interactions between intrauterine tobacco smoke exposure and one SNP located near the gene *EPB41L3* (erythrocyte membrane protein band 4.1-like 3, 18p11) that is involved in intercellular junctions, and might play a role in apoptosis; and exposure to passive smoking in childhood and a SNP localized in *PACRG* gene (PARK2 co-regulated, 6q25.2–q27), which has a role in morphogenesis and ciliary mobility.

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Table 1. Recent G × E interaction studies on asthma highlighting the study characteristics and major findings

Reference/country	Strategy	Population	Outcome	Exposure	Gene	Main result
Caliskan [3▪▪]/USA, Denmark	Candidate G × E	COAST: 200 children, 6–8 years and COPSAC: 297 children, 7 years	Asthma	HRV/RSV wheezing illness	Chromosomal region 17q21	GE HRV and 17q21
Outdoor air pollution						
MacIntyre [4▪▪]/EU/Canada	Candidate G × E	TAG: Six EU/Canadian birth cohorts	Asthma, wheeze	NO_2	*GSTP1/TNFa*	*GSTP1*–NO_2 interaction on asthma
Hwang [5]/Taiwan	Candidate G × E	TCHS: 295 children with asthma and 3517 controls, 12–14 years	Asthma, wheeze	NO_2, CO, SO_2, $PM_{2.5}$	*GSTM1*, *GSTP1*, *GSTT1*	Interaction between *GSTP1*, and $PM_{2.5}$ and O_3 on asthma and wheezing
Su [6▪]/Taiwan	Candidate G × E, ordered subset information gain analysis, MDR	TCHS: 295 children with asthma and 3517 controls, 12–14 years	Asthma	NO_2, CO, SO_2, PM_{10}, O_3	*TNFα*, *ADRB2*, *EPXH1*, *GSTs*, and *NQO1*	*GSTP1*– PM_{10} interaction on childhood asthma. Indication for a *EPHX1*–NO_2 interaction
Fuertes [7▪]/EU/Canada	Candidate G × E	TAG: Six EU/Canadian birth cohorts	Allergic rhinitis	NO_2, $PM_{2.5}$, O_3	*GSTP1*, *TNF*, *TLR2*, *TLR4*	No evidence for G × E interaction
Smoking exposure						
Scholtens [8▪▪]/Europe	GEWIS	Discovery samples: 3048 cases and 3509 control individuals derived from 9 studies (GABRIEL Consortium). Replication samples: four independent studies including more than 13 000 individuals	Childhood-onset asthma	In utero and childhood tobacco smoke	538 233 SNPs	Interaction between in-utero exposure and rs8094633 near *EPB41L3*, and between rs1575472 near *PACRG* and childhood tobacco exposure
Blekic [9▪]/Croatia	Candidate G × E	423 Children with asthma and 414 controls, 5–18 years	Asthma, exacerbations, lung function in asthmatics	ETS and furry pets	Chromosomal region 17q12–21	Most of the interactions did not remain significant after correction for multiple testing
Kljaic-Bukvic [10]/Croatia	Candidate G × E	423 Children with asthma and 414 controls, 5–18 years	Asthma, exacerbations, lung function in asthmatics	Early-life ETS	Chromosomal region 20p13–p12 (*ADAM33* and flanking genes)	Interaction between 23 SNPs and early-life ETS exposure in relation to lung function measures
Li [11]/Taiwan	Candidate G × E	218 Children with asthma and 877 controls (school-aged)	Asthma	Maternal smoking and numbers of household smokers	*ICAM1*(rs5491 and rs5498, and haplotypes)	Interaction between rs5491 or rs5498 and heavy ETS on asthma

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Wang [12]/ Taiwan	Candidate G × E	299 Children with asthma and 383 healthy controls, 5–12 years	Asthma	Household smoking, number of cigarettes smoked by the parents, duration of exposure	*CDH1*, *MMP-3*, and *TIMP-1*	Some evidence for interaction between *CDH1* C-160A and more ETS exposure
Wu [13▪▪]/UK	Candidate G × E, follow-up	807 Children (1–11 years old)	Ever/current wheeze	Maternal current smoking at each follow-up (1, 3, 5, 8 and 11 years), and ETS exposure in infancy (birth or age 1 year)	*GSTP1*, *GSTT1*, and *GSTM1*	The risk of wheezing in the first year of life was significantly increased in *GSTP1* (rs1695, functional) AA homozygotes, but only if their mothers smoked
Kahr [14]/Denmark	Twin study (the Danish Twin Registry)	850 Monozygotic and 2279 like-sex dizygotic twin pairs, 3–9 years	Atopic dermatitis, asthma and hay fever	Cesarean section and in-utero exposure to passive smoking	Heritability in exposed twins compared with unexposed twins	No evidence for interaction
Ferry [15]/Australia	Candidate G × E	1085 Individuals with physician-diagnosed asthma and disease onset at or after age 2	Asthma age-of-onset	Parental and maternal smoking behaviors, household exposure to pets and carpet	26 SNPs that have been associated with the risk of asthma or other allergic diseases in GWAS at the genomewide significance level	No evidence of interaction after correction for multiple testing
Miyake [16]/Japan	Candidate G × E	Prospective prebirth cohort (KOMCHS): 89 women with asthma and 700 controls (mean age 30 years)	Current asthma	Ever smoking	*IL3* (rs40401)	Individuals with the CC genotype who had ever smoked had a 2.67-fold increased risk of asthma in comparison with those with at least one T allele who had never smoked
Other environmental exposures						
Smit [17▪▪]/Europe	Candidate G × E	6025 Adults from ECRHS, Sapaldia, EGEA, B58C and occupational cohorts	Adult-onset asthma	Occupational exposure to high molecular weight allergens	*HLA-II*	Modest interaction between DPB1*03:01 allele and occupational allergen exposure, in particular latex exposure
Shaheen [18▪▪]/UK	Mendelian randomization	5301 Mother–child pairs from the population-based ALSPAC birth cohort, child outcomes at 7 years	Wheezing, asthma, atopy, eczema, hay fever, IgE	Prenatal alcohol exposure	*ADH1B*	No evidence that alcohol exposure *in utero* increases the risk of atopic disease in the offspring

(*Continued*)

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Table 1 (*Continued*)

Reference/country	Strategy	Population	Outcome	Exposure	Gene	Main result
Kljaic-Bukvic [19▪]/Croatia	Candidate G × E	417 Individuals with asthma, 407 controls (age 5–18 years)	Hospitalization for asthma exacerbations	Endotoxin exposure	*CD14*, *LY96*, and *TLR4*	Evidence for interaction between the SNP rs2915863 (*CD14*) and the SNP rs17226566 (in *LY96*) and endotoxin exposure on hospital admission because of asthma exacerbation
Amaral [20▪▪]/ Europe	Candidate G × E	ECRHS II: 2208 European adults with complete data on BHR and *GSTM1*	BHR	Using gas for cooking	*GSTM1*, *GSTP1*, *GSTT1*	Increased bronchial responsiveness was associated with gas cooking among individuals with the *GSTM1* null genotype
Tischer [21▪]/ Europe	Candidate G × E	14 595 children from LISAplus, GINIplus, BAMSE, PIAMA, CAPPS, or ALSPAC	Early wheezing, early asthma symptom complex school-age asthma symptom complex nasal symptoms, rhinoconjunctivitis, and allergic sensitization	Parent-reported mould and dampness in any room of the home during the first 2 years of life	*GSTP1*	No significant interaction
Tsai [22▪]/Taiwan	Candidate G × E	TCHS, 3577 children	Asthma phenotypes	Carpet (indoor allergens)	*IL13*	*IL13* haplotype–carpet interaction for late-onset asthma and wheeze

ALSPAC, Avon Longitudinal Study of Parents and Children; *EPHX1*, epoxide hydrolase 1; ETS, environmental tobacco smoke; G × E, gene–environment; ICAM1, intercellular adhesion molecule 1; MDR, multifactor dimensionality reduction; NO_2, nitrogen dioxide; O_3, ozone; SO_2, sulfur dioxide; TAG, traffic, asthma, and genetics; TCHS, Taiwan Children Health Study.

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Among Croatian schoolchildren aged 5–18 years (423 with asthma and 412 without), Blekic *et al.* [9▪] investigated the increased risk of asthma conferred by 17q12–21 genetic variants, suggesting the involvement of one novel SNP in the IKAROS family zinc finger 3 (*IKZF3*) gene that is involved in the regulation of lymphocyte development. The authors also reported interaction between genetic variants in sphingolipid biosynthesis regulator 3 (*ORMDL3*), gasdermin A (*GSDMA*), gasdermin B (*GSDMB*) and *IKZF3*, and early-life environmental tobacco smoke (ETS) exposure in relation to asthma, hospital admissions, and lung function. In the same population, Kljaic-Bukvic *et al.* [10] investigated the increased risk of asthma conferred by 20p13–p12 genetic variants, and showed that the risk was increased by early-life exposure to ETS for six SNPs in ADAM metallopeptidase domain 33 (*ADAM33*), attractin (*ATRN*), heat-shock 70 kDa protein 12B (*HSPA12B*), and sialic-acid-binding Ig-like lectin 1, sialoadhesin (*SIGLEC1*) genes. In the study by Li *et al.* [11], interactive effects between two functional SNPs (rs5491, rs5498) of intercellular adhesion molecule 1 (*ICAM1*, 19p13.3–p13.2) and ETS exposure were studied among elementary-school children in Taiwan. The risk for asthma was significantly higher among children who simultaneously carried the rs5491 AT or TT genotype and the rs5498 GG genotype. Furthermore, the risk for asthma was much higher in children exposed to heavy ETS (at least two household smokers) and carrying the rs5491 AT or TT genotype or the rs5498 GG genotype. Another study [12] that considered the intensity of ETS exposure found a weak joint effect of exposure to ETS (>5 versus 0 cigarettes per day in early life) and one SNP in the gene *CDH1* (cadherin 1, type 1, E-cadherin, and 16q22) that has an essential role in the formation of epithelial junction. Wu *et al.* [13▪▪] observed a time-dependent interaction between variants in genes from the GST family (*GSTP1*, *GSTM1*, *GSTT1,* and glutathione S-transferase theta 1) and maternal smoking in relation to the development of wheezing in childhood. Their results suggest that *GSTP1* rs1695 A (Ile105) is a risk allele for wheeze, with an effect most clearly seen in children who are exposed to maternal smoking, and only observed for early-life wheezing. In a study [14] based on all live-born twins in Denmark between 1994 and 2000, maternal smoking during pregnancy increased the risk of asthma by 70% in the offspring, but no evidence of genetic effect modification was observed as only a 3% change in the heritability of asthma was observed in children whose mothers smoked during pregnancy compared with children of nonsmoking mothers.

Among 1085 unrelated individuals with asthma and an onset of asthma at or after 2 years of age, Ferry *et al.* [15] investigated the interactions between 26 selected SNPs from GWAS and parental and maternal smoking behavior on the age of asthma onset. The strongest interactions were observed between rs9500927 in *HLA-DOA* (major histocompatibility complex, class II, DO alpha, 6p21.3) and paternal smoking, and between rs10508372 in *LOC338591* (coiled-coil–helix-coiled–coil–helix domain containing 3 pseudogene, 10p14) and both paternal smoking and direct exposure to paternal smoking. The authors also reported interaction between rs4129267 in interleukin-6 receptor (*IL6R*, 1q21) and carpet exposure. There were no significant G × E interactions after correction for multiple testing.

In adults, one study [16] reported an interaction between *IL3* rs40401 [interleukin-3 (colony-stimulating factor, multiple), 5q23–q31] and ever smoking (at least once per day for at least 1 year) on the risk of asthma in 89 cases and 700 healthy, young, Japanese women.

Overall, recent genes by smoking interaction studies on asthma in adults are scarce. Recent findings add to the body of evidence that maternal and parental smoking during pregnancy and in childhood increases the risk of asthma, involving both direct effects and interactive effects with genetics that may vary with time. Indeed, time is a factor known to play a major role in the pathophysiology of asthma, so extending the research from two-dimensional G × E to three-dimensional gene–environment–time interactions may help in discovering novel G × E interactions.

Other environmental exposures

Several recent studies investigated the interactions between candidate genes and other environmental factors associated with asthma, such as occupational allergen exposure, prenatal alcohol exposure, and indoor exposures (endotoxin, mould, gas cooking, and household carpet use).

Evidence from several independent GWAS lends support to the involvement of HLA-II loci in asthma, in particular among adults. Imputed common HLA-II alleles were not associated per se with adult-onset asthma in a meta-analysis of more than 6000 European individuals from cohorts participating in the GABRIEL GWAS [17▪▪]. However, when taking occupational allergen exposures into account, results suggested a G × E interaction between the *DPB1∗03:01* allele and occupational exposure to latex.

Using a Mendelian randomization approach, Shaheen *et al.* [18▪▪] did not find evidence to suggest that alcohol consumption in pregnancy increases the risk of childhood atopic disease. A

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maternal *ADH1B* (alcohol dehydrogenase) variant (rs1229984), as a proxy for prenatal alcohol exposure, was unrelated to childhood asthma and other atopic outcomes. Moreover, there was no interaction between maternal *ADH1B* and reported intake of alcohol in pregnancy.

The complex, but well described interaction between *CD14* (cluster of differentiation 14) variants and endotoxin exposure levels was illustrated again recently among patients with asthma. This study [19▪] observed significant interactions between variants in the endotoxin pathway (*LY69*, lymphocyte antigen 96, and *CD14*) and endotoxin exposure in relation to repeated hospital admissions. However, in the first GEWIS on asthma, Ege *et al.* [25] did not identify any statistically significant interactions with farm exposures at the genomewide level. Moreover, they did not confirm the interactions with SNPs in candidate genes, such as *CD14*, even when a less stringent significance threshold was applied. House dust endotoxin levels were not studied in the GEWIS, which may explain the discrepancy with other findings.

Gas cooking is a major indoor source of the highly oxidant NO_2. In adults from the multicentre European Community Respiratory Health Survey, increased bronchial responsiveness was associated with gas cooking, but only among individuals with the *GSTM1* null genotype [20▪▪]. A meta-analysis of six birth cohorts found statistically significant effects of early exposure to mould or dampness on early wheezing and nasal symptoms, but there was no evidence of a G × E interaction between *GSTP1* (rs1695) and mould exposure [21▪]. Household carpet use is known to be a reservoir of major indoor allergens, which may increase airway inflammation and asthma in children. In the population-based Taiwan Children Health Study [22▪], household carpet use appeared to modify the effects of *IL-13* variants on wheeze and late-onset asthma.

METHODS IN GENE–ENVIRONMENT INTERACTION STUDIES

The G × E studies presented in this review offer a good example on how candidate-gene approaches can complement and help in validating GWAS findings. In fact, thanks to the availability of results from GWAS, new hypotheses were tested including genes implicated in the previously unexplored biological pathways in the study of asthma. Up to now, only two GEWIS on asthma have been conducted [8▪▪,25], which identified overall only two statistically significant interactions. One of the reasons why GEWIS were less successful than the candidate approach in identifying G × E interactions is related to the large number of tests that need to be performed, which in turn requires stringent thresholds in order to declare a G × E interaction significant. Research is moving on to new methods that efficiently estimate the interactions [26▪▪]. As an example, Hancock *et al.* [27] showed that joint testing of SNP and SNP-by-environment interaction identified novel loci associated with complex traits (e.g. pulmonary function) that are missed when considering only the genetic main effects. Lack of replication in GEWIS may reflect also heterogeneity in environmental exposure assessment as well as in outcome definition. Large consortia of epidemiologic studies with well characterized exposure data and standardized outcome definition are warranted to exploit the potential of G × E interaction studies.

An alternative between the candidate and the 'agnostic' approach of GWAS is provided by the pathway-based approach, in which several genes related to the biological pathways of interest are studied. An enriched gene-set selection strategy that integrates the information on biological processes shared by genes, the canonical pathways to which they belong, and knowledge of the environmental factor has recently been proposed [28▪]. Rare genetic variant association, together with the G × E interaction studies, is believed to be another important contributor to missing heritability [29]. Thanks to the advent of next-generation sequencing technologies and whole-exome arrays, it is now possible to genotype rare variants at relatively low cost. As the power of traditional methods to detect G × E interactions is expected to be low, specialized association tests and methodologies are now being developed [30].

Together with G × E interaction, gene–gene interactions, or epistasis, and epigenetic effects are believed to be of great importance for the development of complex diseases. In particular, recent findings support the hypothesis that gene–environment interactions in asthma are mediated, at least in part, by epigenetic processes, such as DNA methylation (see the review by Kabesch [31▪▪]). Numerous studies have also provided evidence that both intestinal and airway microbiome, and their alteration may contribute to chronic asthma (reviewed in [32▪]), offering new routes of research into the understanding of G × E interactions. The integration of genetic, epigenetic, and microbiome data may help in clarifying the complex mechanism of asthma pathogenesis.

CONCLUSION

This review shows that most recent G × E interaction studies followed a candidate-gene approach, and only one recent GEWIS study exists on asthma. Research in the genetics of complex diseases is

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moving toward increasingly detailed data. Nevertheless, the success of post-GWAS era studies in asthma will depend also on the effort put into adequate quantification of environmental exposure and standardization in sample collection as well as phenotype definition. Novel genes of susceptibility to asthma were revealed only when relevant environmental exposures were considered. Therefore, it could be envisaged that detecting G × E interactions may help to target the preventive strategies in susceptible individuals.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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A G × E interaction detected with a multifactor dimensionality reduction approach.

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A study that explored the interactions between exposure to traffic-related air pollutants and candidate genes on allergic rhinitis and allergic sensitization in children from six birth cohort studies.

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This study on childhood asthma is the first hypothesis-free GEWIS, specifically aiming to identify SNPs that interact with tobacco smoke exposure in disease development. Suggestive evidence for an interaction between rs8094633 near EPB41L3 and in-utero tobacco smoke exposure, and an interaction between rs1575472 in PACRG and childhood tobacco smoke exposure were found. These SNPs have not been identified previously in general genomewide association studies on childhood asthma.

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In a birth cohort study, interactions between maternal smoking and GST variants on wheezing during the first 11 years of life were investigated. Results provide evidence that children carrying GSTP1 rs1695 AA may be more susceptible to the effects of maternal smoking regarding the development of wheeze at a young age, and that the effect of maternal smoking on wheezing diminishes with time.

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This excellent analysis in the large population-based ALSPAC birth cohort used a Mendelian randomization approach to study the relation between prenatal alcohol exposure and atopic phenotypes. This approach, which minimizes bias and confounding, did not provide evidence to suggest that prenatal alcohol exposure increases the risk of asthma or atopy in childhood.

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