Childhood allergic rhinitis, traffic-related air pollution, and variability in the *GSTP1*, *TNF*, *TLR2*, and *TLR4* genes: Results from the TAG Study

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Background: Associations between traffic-related air pollution (TRAP) and allergic rhinitis remain inconsistent, possibly because of unexplored gene-environment interactions.
Objective: In a pooled analysis of 6 birth cohorts (N_{total} = 15,299), we examined whether TRAP and genetic polymorphisms related to inflammation and oxidative stress predict allergic rhinitis and sensitization.
Methods: Allergic rhinitis was defined with a doctor diagnosis or reported symptoms at age 7 or 8 years. Associations between nitrogen dioxide, particulate matter 2.5 ($PM_{2.5}$) mass, $PM_{2.5}$

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absorbance, and ozone, estimated for each child at the year of birth, and single nucleotide polymorphisms within the *GSTP1*, *TNF*, *TLR2*, or *TLR4* genes with allergic rhinitis and aeroallergen sensitization were examined with logistic regression. Models were stratified by genotype and interaction terms tested for gene-environment associations.
Results: Point estimates for associations between nitrogen dioxide, $PM_{2.5}$ mass, and $PM_{2.5}$ absorbance with allergic rhinitis were elevated, but only that for $PM_{2.5}$ mass was statistically significant (1.37 [1.01, 1.86] per 5 $\mu g/m^3$). This result was not robust to single-cohort exclusions. Carriers of at least 1 minor rs1800629 (*TNF*) or rs1927911 (*TLR4*) allele were consistently at an increased risk of developing allergic rhinitis (1.19 [1.00, 1.41] and 1.24 [1.01, 1.53], respectively), regardless of TRAP exposure. No evidence of gene-environment interactions was observed.
Conclusion: The generally null effect of TRAP on allergic rhinitis and aeroallergen sensitization was not modified by the studied variants in the *GSTP1*, *TNF*, *TLR2*, or *TLR4* genes. Children carrying a minor rs1800629 (*TNF*) or rs1927911 (*TLR4*) allele may be at a higher risk of allergic rhinitis.
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Key words: *Childhood allergic rhinitis, air pollution, genetics, interaction, TNF, TLR4*

Abbreviations used

APMoSPHERE:	Air Pollution Modelling for Support to Policy on Health and Environmental Risk in Europe
BAMSE:	Children, Allergy, Milieu, Stockholm, Epidemiological Survey
CAPPS:	Canadian Asthma Primary Prevention Study
GINIplus:	German Infant study on the influence of Nutritional Intervention plus environmental and genetic influences on allergy development
GSTP1:	Glutathione-*S*-transferase pi 1
LISAplus:	Lifestyle related factors, Immune System and the development of Allergies in Childhood plus the influence of traffic emissions and genetics study
LUR:	Land-use regression
NO_2:	Nitrogen dioxide
OR:	Odds ratio
PIAMA:	Prevention and Incidence of Asthma and Mite Allergy
PM:	Particulate matter
SAGE:	Study of Asthma, Genes, and Environment
SNP:	Single nucleotide polymorphism
TAG:	Traffic, Asthma, and Genetics
TLR:	Toll-like receptor
TRAP:	Traffic-related air pollution

Recent global estimates indicate that 8.5% of children aged 6 to 7 have allergic rhinitis, and the prevalence is higher among 13 to 14 year olds (14.6%).[1] The continued increase in prevalence in recent years in a majority of countries is especially concerning.[2] Allergen exposure is strongly associated with allergic rhinitis onset. Early-life factors (young maternal age, multiple gestation, and low birth weight), family history, ethnicity, and environmental factors (environmental tobacco smoke, urban living, lifestyle, nutrition, air pollution) are also believed to be important.[3-5]

Substantial experimental and toxicologic evidence of the adverse effects of traffic-related air pollution (TRAP) on allergic disease exists, and epidemiologic evidence is building,[6] as summarized in a recent review.[7] Given its association with asthma, TRAP has been investigated as a potential cause of allergic rhinitis, and several recent large studies support a positive association.[8,9] However, some studies have failed to find an association between the prevalence of allergic rhinitis symptoms and exposure to air pollution.[10-12]

Whether TRAP increases the risk of allergic disease development and exacerbates symptoms in a genetically vulnerable subgroup remains largely unknown.[7,13] Gene-environment interactions, which have been rarely considered in previous studies of allergic rhinitis, may provide some insight and have thus been recommended.[14] Many studies that examined the interplay between genetic susceptibility and TRAP on respiratory conditions have focused on genes in the oxidative stress and inflammation pathways.[15]

Genetic variants of the glutathione-*S*-transferase pi 1 (*GSTP1*) gene have sparked considerable interest, given the existence of common functional variants in the general population, the role of *GSTP1* in cellular protection against oxidative stress, and the presence of the cytosolic glutathione-*S*-transferase proteins in the human lung.[16] The evidence of a gene-environment interaction appears strongest for the Ile105Val (rs1695) single nucleotide polymorphism (SNP) within the *GSTP1* gene.[17-23] Gene-environment interactions have also been observed for the G308A (rs1800629) SNP within the *TNF* gene for passive smoke exposure and childhood asthma[24] and for ozone exposure with lung function and wheezing.[25,26] Furthermore, a gene-gene-environment interaction between the G-308A *TNF* variant, *GSTP1* variants, and nitrogen dioxide (NO_2) exposure was documented for allergic outcomes.[23] Members of the Toll-like receptor (*TLR*) family may also be important, given their key roles in controlling innate and adaptive immune responses. Genetic polymorphisms in *TLR*s have already been associated with allergic rhinitis[27] and may modify the link between particulate matter and childhood asthma.[28]

With the use of a pooled analysis that combined data from 6 birth cohorts with individual-level assessment of air pollution exposure, we examined the association among TRAP, allergic rhinitis, and aeroallergen sensitization in children and the influence of 10 SNPs related to inflammation and oxidative stress metabolism in the *GSTP1, TNF, TLR2,* and *TLR4* genes.

METHODS

Data sources

The Traffic, Asthma, and Genetics (TAG) study population is composed of 15,299 children recruited in 6 birth cohorts: the Canadian Asthma Primary Prevention Study (CAPPS),[29] the Study of Asthma, Genes, and Environment (SAGE),[30] the Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE),[31,32] the Prevention and Incidence of Asthma and Mite Allergy study (PIAMA),[33] the German Infant Nutritional Intervention study (GINIplus),[34] and the Lifestyle related factors, Immune System and the development of Allergies in Childhood study (LISAplus).[35] Data on several health outcomes, environmental exposures, and covariates were collected via either parent- or self-completed questionnaires at various time points according to each cohort's respective information collection strategy. Information across cohorts was harmonized into common variables. A detailed description of this harmonization process and the recruitment and follow-up of each cohort is provided elsewhere (MacIntyre et al, submitted 2012).

Assessment of outcomes

The assessment of allergic rhinitis differed slightly across cohorts; the 2 Canadian cohorts (CAPPS and SAGE) relied on a diagnosis during an