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ORIGINAL ARTICLE

Retrospective Study

Interactions between traffic air pollution and glutathione S-transferase genes on childhood asthma

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Abstract

AIM: To evaluate the role of glutathione S-transferase P1 (*GSTP1*) genetic polymorphisms potentially modifying the association between NO_2 and asthma/wheeze in Taiwanese children.

METHODS: We investigated 3714 schoolchildren in Taiwan Children Health Study from 14 communities. Children's information was measured from questionnaire by parents. The traffic air pollutant was available from Environmental Protection Administration monitoring stations.

RESULTS: A two-stage hierarchical model and a multiple logistic regression model were fitted to estimate the effects of NO_2 exposures and GSTs polymorphisms on the prevalence of asthma and wheeze. Among children with *GSTP1* Ile/Val or Val/Val genotypes, those residing in high-NO_2 communities had significantly increased risks of asthma (OR = 1.76, 95%CI: 1.15-2.70), late-onset asthma (OR = 2.59, 95%CI: 1.24-5.41), active asthma (OR = 1.93, 95%CI: 1.05-3.57), asthma under medication (OR = 2.95, 95%CI: 1.37-6.32) and wheeze (OR = 1.54, 95%CI: 1.09-2.18) when compared with children in low-NO_2 communities. Significant interactions were noted between ambient NO_2 and *GSTP1* on asthma, late-onset asthma, asthma under medication and wheeze (*P* for interaction < 0.05). However, we did

not find any association with polymorphisms in *GSTM1* and *GSTT1*.

CONCLUSION: Children under high traffic air pollution exposure are more susceptible to asthma, especially among those with *GSTP1* Val allele.

Key words: Nitrogen dioxide; *GSTP1*; Asthma; Wheeze; Children

Core tip: Children under high traffic air pollution exposure are more susceptible to asthma, especially among those with glutathione S-transferase P1 (*GSTP1*) Val allele. This relatively common genetic polymorphism thus may play an important role in asthma pathogenesis among children depending on airway oxidative stress generation.

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INTRODUCTION

The prevalence of childhood asthma/wheeze has been increasing around the world[1-4], potentially leading to increased medical costs and social burden[5]. Asthma is a complex, multifactorial disease that includes a number of environmental and genetic components[6,7]. Although gene-environment interactions are likely to be important in both the etiology and aggravation of asthma in children, few studies have examined the interactive associations between childhood exposure to common air pollutants, such as ambient NO_2, and common genetic polymorphisms that might be involved in asthma susceptibility.

Traffic-related air pollution, such as ambient nitrogen dioxide (NO_2), has been demonstrated to increase risks for childhood asthma[8-10] and bronchitic symptoms[11,12] and results in diminished pulmonary function development[13,14]. NO_2 is a key component of automobile emissions and is frequently used as an indicator of exposure to traffic-related air pollution[9,15]. NO_2 has relatively strong oxidation potential and can lead to pulmonary epithelial cells injury[16,17]. Polymorphisms in antioxidative genes are likely to play important roles in mediating oxidative stress and thus could influence inflammatory response. Members of glutathione S-transferases (GSTs) have been extensively studied for gene-environment interactions, because of their ability to conjugate hazardous reactive oxygen species (ROS) with glutathione, and the high prevalence of variant alleles[18-21].

The Taiwan Children Health Study (TCHS) is a population-based study representing a wide range of environmental factors and genetic susceptibility. TCHS offers an opportunity to investigate the potential contributions of gene-environment interactions to respiratory health. In the present study, we evaluated the role of GSTs genetic polymorphisms as potential modifiers of the association between ambient NO_2 and asthma/wheeze in children.

MATERIALS AND METHODS

Study population

We conducted a population-based survey for children's health in 2007; the study protocol has been described in detail previously[11,22]. The parents or guardians of each participating student provided written informed consent at study entry. Briefly, the TCHS recruited 5082 7th and 8th-grade schoolchildren from 14 diverse communities that were selected with the aim of maximizing the variability and minimizing the correlations of exposures to outdoor pollutants based on historic routine air monitoring data in Taiwan. We excluded 37 subjects with active smoking habits in risk factor determination, due to sample size limitation for stratification analyses. In this analysis, we randomly selected 3714 seventh-grade children to provide buccal cells as the DNA resource for genotyping. The study protocol was approved by the institutional review board (National Taiwan University Hospital Research Ethics Committee).

Questionnaire of asthma phenotypes

The standard questionnaire for childhood exposures and health status was taken home by students and answered by parents or guardians. Children were considered to have asthma if there was a positive answer to the question "Has a doctor ever diagnosed this child as having asthma?" Wheeze was defined as any occurrence of the child's chest sounding wheezy or whistling. Early-onset asthma was defined as age of onset for asthma before 5 years of age. Late-onset asthma was onset after 5 years of age. Active asthma was defined as physician-diagnosed asthma with any asthma-related symptoms or illness in the previous 12 mo. Asthma under medication was defined as use of any inhaled, oral, or intravenous medication in the past 12 mo.

Traffic air pollution and other covariates

The monitoring data of traffic air pollutant, NO_2, are available from 14 Environmental Protection Administration monitoring stations in Taiwan. Concentrations of NO_2 were measured continuously by chemiluminescence and reported hourly. The yearly averaged concentration was calculated from the daily (24-h) NO_2 in each community. We used the annual average of ambient NO_2 levels from 2005 through 2007 to response the

Table 1 Primer and probe sequences for *GSTP1*, *GSTM1* and *GSTT1* genes variants

Gene	Sequence
GSTP1 (Ile105Val)	
Forward primer	5′-CCTGGTGGACATGGTGAATG-3′
Reverse primer	5′-TGCTCACATAGTTGGTGTAGATGA-3′
Prob for Ile allele	5′-(VIC)CTGCAAATACGTCTCC-3′
Prob for Val allele	5′-(6FAM)TGCAAATACATCTCCCT-3′
GSTM1	
Forward primer	5′-GGAAACAAGGTAAAGGAGGAGTGAT-3′
Reverse primer	5′-CAAGAATATGTGGGCTGGAACCT-3′
Prob	5′-ACGTGAAGCAAAACAG-3′
GSTT1	
Forward primer	5′-GTGGTCCCCAAATCAGATGCT-3′
Reverse primer	5′-GCACCCACGGGCTGT-3′
Prob	5′-CCCTGCCCTCACAACC-3′

long-term exposure to traffic air pollution. Community-level NO_2 was classified into low and high groups using a median cutoff. The means of high- and low-NO_2 communities were 22.13-ppb and 13.96-ppb respectively.

Basic demographic data and possible confounding exposures were also collected, including sex, age, grade, community, dampness at home, *in utero* exposures to maternal smoking and environmental tobacco smoke (ETS) at home. Dampness at home was determined as any one of the following: Visible mould or perceived mould odor or perceived wet stamps because of moisture in the ceilings, floors or walls in the house.

DNA collection and genotyping

Genomic DNA was isolated from buccal cells collected on cotton swabs containing oral mucosa using phenol/chloroform extraction method. The glutathione S-transferase P1 (*GSTP1*) Ile105Val, *GSTM1 null* and *GSTT1 null* polymorphisms were detected by real-time polymerase chain reaction using the TaqMan Allelic Discrimination assay on an ABI PRISMTM 7900 Sequence Detector (Applied Biosystems, Foster City, CA). The details of primer and probe sequences are presented in Table 1.

Statistical analysis

We used a mixed model approach to estimate the individual effect of NO_2 for community as a random effect variable. Unconditional multiple logistic regression models were fitted to estimate the individual effects of *GSTP1*, *GSTM1* and *GSTT1* on asthma phenotypes. When considering the effects of the variant *GSTP1* allele, we used dominant, co-dominant and additive models. On the basis of *a priori* consideration, we included age, sex, family income and parental education in all models. If estimates of GSTP1 effects on asthma changed by at least 10% when a covariate was included in the base models, then the covariate was included in the final models. The interaction between ambient NO_2 level and genotype was assessed by adding an interactive term in the logistic regression model, and a likelihood ratio test was used to test its significance.

Two-stage methods were used to correct for between-community variances. In the first step, a logistic regression model was used to estimate the adjusted logit of disease frequency in each of the 14 communities, controlling for individual-level confounders. In the second step, these estimated logits were regressed against the community-specific NO_2 measurements using weights that were inversely proportional to the sum of the between-community variance and the within-community variance of the adjusted logits. The association between levels of traffic-related air pollution and prevalence of asthma phenotypes were graphically presented by plotting NO_2 levels on the X-axis and community-specific adjusted prevalence on the Y-axis. The regression curves were drawn through the community-specific prevalence derived from exponential regression models. All analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC, United States).

RESULTS

A total of 3714 children with genotyping data were enrolled in this study, after excluding children with active smoking. The mean age of participants was 12.8 years and all participants were of Han Chinese ethnic origin (Table 2). More than half subjects reported presence of dampness at home, 43.2% had ETS exposure at home, and only 3.8% had maternal smoking exposure during pregnancy. The prevalence rates were 7.8%, 2.6% and 12.0% for lifetime asthma, asthma under medication and wheeze, respectively. The *GSTP1* alleles were in Hardy-Weinberg equilibrium, with 65.5% having the Ile/Ile genotype and 4.0% the Val/Val genotype.

Table 3 showed the main effects for exposure to NO_2, *GSTP1*, *GSTM1* and *GSTT1* genotypes, respectively. After adjustment for potential confounders, ambient NO_2 level tended toward positive associations with all asthma phenotypes, although none of the associations were statistically significant. There were no observed significant genetic effects for any GST polymorphism.

To assess the role of the *GSTP1* gene on the effects of the NO_2 exposure on asthma (Table 4), we fitted models stratifying subjects by their *GSTP1* Ile105Val genotypes. In Ile/Val or Val/Val genotypes, compared with children exposed in low-NO_2 communities, those exposed in high-NO_2 communities had significantly increased risks of asthma (OR = 1.76, 95%CI: 1.15-2.70), late-onset asthma (OR = 2.59, 95%CI: 1.24-5.41), active asthma (OR = 1.93, 95%CI: 1.05-3.57), asthma under medication (OR = 2.95, 95%CI: 1.37-6.32) and wheeze (OR = 1.54, 95%CI: 1.09-2.18). However, there were no significantly associations between NO_2 levels on asthma phenotypes in *GSTP1* Ile/Ile genotypes. We also found significantly interactive effects on asthma, late-onset

Table 2 Selected characteristics for participants in Taiwan children health study *n* (%)

	With genotyping (*n* = 3714)	All eligible participants (*n* = 5045)
Demographic information		
Sex		
Boys	1820 (49.0)	2436 (48.3)
Girls	1894 (51.0)	2609 (51.7)
Age, yr (mean ± SD)	12.8 ± 0.4	12.9 ± 0.6
Parental education, yr[1]		
≤ 12	2301 (62.0)	3176 (63.5)
13-15	734 (19.8)	956 (19.1)
≥ 16	674 (18.2)	873 (17.4)
Gestational age[1]		
Full term	3318 (90.9)	4461 (90.7)
< 4 wk early	236 (6.5)	316 (6.4)
≥ 4 wk early	98 (2.7)	142 (2.9)
Parental history of atopy[1]		
Yes	952 (26.5)	1257 (25.9)
No	2645 (73.5)	3590 (74.1)
Family income[1,2]		
≤ 400000	1233 (35.7)	1751 (37.5)
410000-800000	1402 (40.6)	1844 (39.5)
≥ 810000	822 (23.8)	1072 (23.0)
Number of siblings[1]		
0	346 (9.3)	458 (9.1)
1	1748 (46.9)	2265 (45.0)
2	1229 (33.0)	1697 (33.7)
≥ 3	406 (10.9)	613 (12.2)
Home exposures[1]		
Dampness at home	1915 (51.6)	2610 (51.7)
In utero exposure maternal smoking	141 (3.8)	193 (3.8)
ETS at home	1597 (43.2)	2246 (44.8)
Respiratory outcomes[1]		
Asthma	289 (7.8)	372 (7.4)
Asthma under medication	95 (2.6)	122 (2.4)
Wheeze	443 (12.0)	583 (11.6)
Early-onset asthma	186 (5.2)	239 (4.9)
Late-onset asthma	95 (2.7)	121 (2.5)
Active asthma	136 (3.7)	168 (3.4)
Genetic markers[1]		
GSTP1		
Ile/Ile	2433 (65.5)	
Ile/Val	1132 (30.5)	
Val/Val	149 (4.0)	
GSTM1		
Present	1596 (43.0)	
Null	2118 (57.0)	
GSTT1		
Present	1923 (51.8)	
Null	1791 (48.2)	

[1]Number of subjects do not add up to total N because of missing data; [2]New Taiwan dollars per year ($1 US = $ 33 New Taiwan). ETS: Environmental tobacco smoke.

asthma, asthma under medication and wheeze (*P* for interaction < 0.05). However, there were no significant relationships between NO_2 level and *GSTM1* and *GSTT1* genotypes on asthma and wheeze (Tables 5 and 6).

We also calculated the adjusted community-specific prevalence of asthma and wheeze, stratified by *GSTP1* genotypes (Figure 1). Children with *GSTP1* Val allele had a higher prevalence of asthma if they lived in communities with higher NO_2.

DISCUSSION

In this study, we found that, overall, children exposed to ambient NO_2 level tended toward increased risks on asthma phenotypes. None of the main effects of the various GST genotypes were significant, and neither the *GSTM1* nor *GSTT1 null* polymorphisms showed any significant modifying effect of ambient NO_2 on childhood asthma. However, in children with *GSTP1* Val alleles, those resided in high-NO_2 communities had significantly increased risks of asthma-related diseases.

Although the genetic main effects of GSTs were not significant, *GSTP1* was noted to modify the effects of ambient NO_2 on childhood asthma. In children with *GSTP1* Val alleles, those resided in high-NO_2 communities had significantly increased risks of asthma, late-onset asthma, active asthma, asthma under medication and wheeze.

Age, sex, parental education and family income have been suggested as personal and social confounders for contributing to asthma and wheeze in childhood. Exposure to other residential factors, such as number of siblings, parental atopic history, *in utero* exposures to maternal smoking, ETS exposure at home, dampness at home, gestational age, history of any pets and air cleaner use were also considered in our survey. However, some covariates were not includes in the final model because of less than 10% change in point estimates in the statistical procedures. One strength of this study is that we minimized interference from these confounders by recruiting lifelong non-smokers of similar age at study entry, and adjusting these potential confounders by regression models. An additional strength of the study is that all of the schools were chosen in the vicinity of monitoring stations. Almost all children attending their schools generally lived within walking distance, because the density of middle schools is very high in Taiwan. Children usually spend at least 8 h in schools and there are few air-conditions in classrooms. Outdoor air-pollutants generated by nearby traffic have been reported to readily penetrate indoors[23]. A potential weakness of this study is that we did not have individual exposure measurements for traffic-related air pollutants, but rather relied on air pollution monitoring data to represent both school and home exposure. However, two-stage regressions were used to consider the community-level and individual-level exposure to reduce potential ecological bias.

Although not statistically significant as a main effect, our data suggested that increased exposure to ambient NO_2 was positive related to asthma phenotypes (Table 3). This is consistent with previous studies, where NO_2 levels measured from monitoring stations were reported to be associated with an increased incidence of asthma in a Japan cohort[24] and with wheeze prevalence in United States[25]. Gauderman and coworkers also suggested that residential distance to a freeway and model-based estimates of freeway traffic-

Table 3 Association of ambient NO_2 and glutathione S-transferases genotypes with asthma phenotypes

	Asthma		Early-onset asthma		Late-onset asthma		Active asthma		Asthma under medication		Wheeze	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
NO_2	1.03	(0.80, 1.32)	1.03	(0.76, 1.39)	1.1	(0.72, 1.66)	1.16	(0.82, 1.65)	1.33	(0.87, 2.03)	1.08	(0.88, 1.32)
GSTP1												
Co-dominant model												
Ile/Ile	1		1		1		1		1		1	
Ile/Val	0.98	(0.75, 1.28)	0.99	(0.71, 1.38)	1.01	(0.64, 1.61)	1.01	(0.69, 1.49)	0.94	(0.59, 1.49)	1.03	(0.82, 1.28)
Val/Val	0.80	(0.41, 1.57)	0.50	(0.18, 1.39)	1.47	(0.62, 3.51)	1.07	(0.45, 2.54)	1.30	(0.50, 3.34)	0.99	(0.59, 1.66)
Dominant model												
Ile/Ile	1		1		1		1		1		1	
Ile/Val or Val/Val	0.96	(0.74, 1.24)	0.93	(0.68, 1.29)	1.07	(0.69, 1.66)	1.02	(0.70, 1.48)	0.98	(0.63, 1.52)	1.02	(0.82, 1.27)
Additive model												
Val allele	0.95	(0.76, 1.18)	0.89	(0.67, 1.17)	1.11	(0.78, 1.58)	1.02	(0.75, 1.39)	1.02	(0.71, 1.48)	1.01	(0.85, 1.21)
GSTM1												
Null	0.89	(0.69, 1.13)	0.83	(0.62, 1.13)	0.94	(0.62, 1.43)	0.88	(0.62, 1.26)	0.81	(0.54, 1.23)	0.99	(0.81, 1.22)
GSTT1												
Null	1.18	(0.92, 1.51)	1.29	(0.95, 1.75)	1.04	(0.69, 1.58)	1.43	(1.00, 2.03)	1.47	(0.96, 2.23)	1.16	(0.95, 1.42)

Models are adjusted for age, sex, family income, parental education, parental history of atopy, number of siblings, *in utero* exposures to maternal smoking, environmental tobacco smoke at home, gestational age and dampness at home.

Table 4 Association of ambient NO_2 level with asthma phenotypes, stratified by *GSTP1* genotypes

	GSTP1				*P* for interaction
	Ile/Ile		Ile/Val or Val/Val		
	OR	95%CI	OR	95%CI	
Asthma					
Low NO_2	1		1		0.003
High NO_2	0.78	(0.57, 1.06)	1.76	(1.15, 2.70)	
Early-onset asthma					
Low NO_2	1		1		0.10
High NO_2	0.88	(0.60, 1.29)	1.45	(0.86, 2.47)	
Late-onset asthma					
Low NO_2	1		1		0.01
High NO_2	0.63	(0.37, 1.07)	2.59	(1.24, 5.41)	
Active asthma					
Low NO_2	1		1		0.06
High NO_2	0.89	(0.57, 1.39)	1.93	(1.05, 3.57)	
Asthma under medication					
Low NO_2	1		1		0.02
High NO_2	0.88	(0.52, 1.49)	2.95	(1.37, 6.32)	
Wheeze					
Low NO_2	1		1		0.01
High NO_2	0.90	(0.69, 1.16)	1.54	(1.09, 2.18)	

Models are adjusted for age, sex, family income, parental education, parental history of atopy, number of siblings, *in utero* exposures to maternal smoking, environmental tobacco smoke at home, gestational age and dampness at home.

emission exposure at homes were both associated with the prevalence of childhood asthma[15]. In that study each of the traffic metrics was also correlated with measured concentrations of NO_2, and measured NO_2 was associated with asthma. Other studies with direct residential measurement or with exposure assessment models of ambient NO_2 have generally shown associations with asthma and asthma-related outcomes among children[26,27]. In Taiwan, we have previously reported that the risk of childhood asthma was positively associated with NOx[28] and an increase of 8.79 ppb of ambient NO_2 exposure would result in 80% increase in the prevalence of bronchial symptoms[11]. *In vitro* and experimental human studies have also demonstrated that high concentrations of NO_2 exposure can result in cell damage accompanied by release of cytokines[29] and may lead to an increase in early and late asthmatic response after challenge with house dust mite allergen compared with ordinary air[30]. Although low ambient concentration of NO_2 exposure was usual,

Table 5 Association of ambient NO_2 level with asthma phenotypes, stratified by *GSTM1* genotypes

	GSTM1				*P* for interaction
	Present		Null		
	OR	95%CI	OR	95%CI	
Asthma					
Low NO_2	1		1		0.87
High NO_2	1.11	(0.76, 1.60)	0.98	(0.70, 1.38)	
Early-onset asthma					
Low NO_2	1		1		0.79
High NO_2	1.02	(0.65, 1.59)	1.01	(0.66, 1.54)	
Late-onset asthma					
Low NO_2	1		1		0.68
High NO_2	1.33	(0.71, 2.50)	1.02	(0.58, 1.78)	
Active asthma					
Low NO_2	1		1		0.97
High NO_2	1.18	(0.69, 2.01)	1.16	(0.72, 1.87)	
Asthma under medication					
Low NO_2	1		1		0.61
High NO_2	1.16	(0.62, 2.16)	1.50	(0.84, 2.69)	
Wheeze					
Low NO_2	1		1		0.75
High NO_2	1.05	(0.76, 1.44)	1.10	(0.84, 1.44)	

Models are adjusted for age, sex, family income, parental education, parental history of atopy, number of siblings, *in utero* exposures to maternal smoking, environmental tobacco smoke at home, gestational age and dampness at home.

Table 6 Association of ambient NO_2 level with asthma phenotypes, stratified by *GSTT1* genotypes

	GSTT1				*P* for interaction
	Present		Null		
	OR	95%CI	OR	95%CI	
Asthma					
Low NO_2	1		1		0.96
High NO_2	1.09	(0.76, 1.57)	0.99	(0.70, 1.39)	
Early-onset asthma					
Low NO_2	1		1		0.39
High NO_2	1.29	(0.82, 2.05)	0.87	(0.58, 1.32)	
Late-onset asthma					
Low NO_2	1		1		0.39
High NO_2	0.96	(0.52, 1.75)	1.24	(0.69, 2.24)	
Active asthma					
Low NO_2	1		1		0.66
High NO_2	1.31	(0.76, 2.28)	1.07	(0.67, 1.71)	
Asthma under medication					
Low NO_2	1		1		0.23
High NO_2	1.96	(1.00, 3.84)	1.03	(0.59, 1.79)	
Wheeze					
Low NO_2	1		1		0.33
High NO_2	1.23	(0.91, 1.66)	0.96	(0.73, 1.28)	

Models are adjusted for age, sex, family income, parental education, parental history of atopy, number of siblings, *in utero* exposures to maternal smoking, environmental tobacco smoke at home, gestational age and dampness at home.

the adverse effects of NO_2 on respiratory outcomes were still important in epidemiologic studies[8,9,31]. As a whole, these results indicated that exposure to outdoor NO_2 or other freeway-related pollutants was a significant risk factor for childhood asthma.

In the present study, we identified a statistically

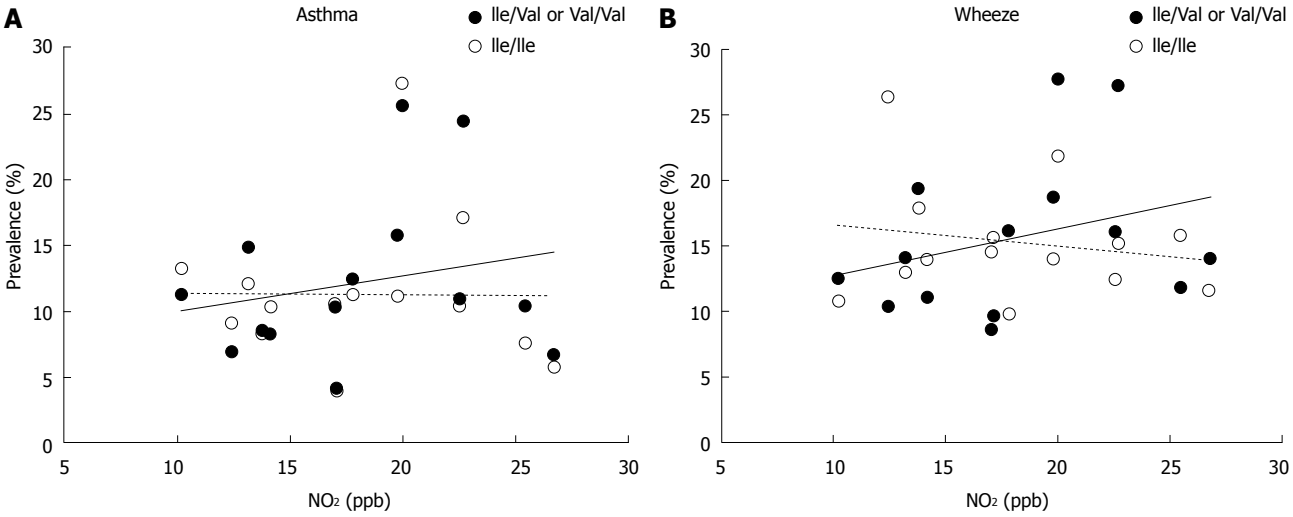

Figure 1 Community-specific prevalence of asthma phenotypes across ambient NO_2 levels, stratified by *GSTP1* genotypes. A: Asthma; B: Wheeze. Solid circles and the solid trend line indicate children with Ile/Val or Val/Val genotypes and hollow circles with the dashed trend line indicate children with Ile/Ile genotype.

significant interactive effect between the *GSTP1* Val allele polymorphism and increased effects of NO_2 on childhood asthma (Table 4). NO_2, a component of ambient air pollution, is an oxidant gas and could lead to pulmonary epithelial cell injury that contributes to a variety of diseases, including asthma[16,17]. The GSTP1-1 enzyme is a phase Ⅱ enzyme that participates in the eliminate ROS by conjugation with glutathione and thus may be an important tissue defense mechanism against oxidative stress[18]. GSTP1 is the most common form of GST found in the respiratory tract lining fluid, representing over 90% of total GST-derived enzyme activity in the lung[19,32]. Our results suggested that children carrying *GSTP1* Val allele and who have exposure to high NO_2 levels may be at increased risks of asthma, because the low GST enzyme activity and high NO_2 levels would increase the oxidant stress in airways (Figure 1).

Thus, our study suggests a gene-environment interaction between the *GSTP1* and NO_2 exposure with individual susceptibility to asthma/wheeze in children. Melen and colleagues also reported that children with *GSTP1* Ile/Val or Val/Val genotypes had an increased risk of sensitization to any allergen when exposed to elevated levels of traffic NOx during the first year of life[33]. In a large birth cohort, children carrying *GSTP1* minor alleles may constitute a susceptible population at increased risk of asthma associated with NO_2 exposure[21]. Previous studies reported that *GSTP1* Val/Val genotype and microsomal epoxide hydroxylase (EPHX1) high activity genotype might contribute to the occurrence of childhood asthma, especially among those who lived near major roads or in high-NO_2 communities[34,35]. Castro-Giner *et al*[36] explored the associations between multiple antioxidant-related genetic polymorphisms, NO_2 and asthma. They only found an association with *NQO1* [NAD(P)H: Quinine oxidoreductase], traffic-related air pollution and asthma in adults, but *GSTs* genetic polymorphisms were not significant. The inconsistent results might be the different ethnic populations and differential age groups.

GSTM1 and *GSTT1* genes are two common deletion polymorphisms and they have been related to asthma in children[19,37,38]. Some studies reported that certain subgroups of children with *GSTM1* null genotype were more susceptible to ozone than others[39,40]. However, we did not identify any other studies that have reported significantly interactive effects between *GSTM1*, *GSTT1* and ambient NO_2 among childhood asthma[36], consistent with our findings in this report (Tables 5 and 6).

In conclusion, our data showed that the high prevalence of childhood asthma was associated with high concentrations of ambient NO_2. Among children with *GSTP1* Val alleles, those with high-NO_2 exposure had significantly increased risks of asthma, late-onset asthma, active asthma, asthma under medication and wheeze. This relatively common genetic polymorphism thus may play an important role in asthma pathogenesis among children depending on airway oxidative stress generation.

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COMMENTS

Background

Ambient traffic-related air pollutants, such as nitrogen dioxide (NO_2), have shown adverse respiratory effects in children. Members of glutathione S-transferases (GSTs) have been extensively studied for gene-environment interactions, because of their ability to conjugate hazardous reactive oxygen

species with glutathione. In this study, the authors evaluated the role of *GST* genetic polymorphisms potentially modifying the association between NO_2 and asthma/wheeze in Taiwanese children.

Research frontiers

Few studies have explored the interactive associations between traffic-related air pollution and genetic polymorphisms on childhood asthma. In this study, the authors identified a statistically significant interactive effect between the glutathione S-transferase P1 (*GSTP1*) Val allele polymorphism and increased effects of NO_2 on childhood asthma in Han Chinese population.

Innovations and breakthroughs

The authors found that the high prevalence of childhood asthma was associated with high concentrations of ambient NO_2. Among children with *GSTP1* Val alleles, those with high-NO_2 exposure had significantly increased risks of asthma, late-onset asthma, active asthma, asthma under medication and wheeze. This relatively common genetic polymorphism thus may play an important role in asthma pathogenesis among children depending on airway oxidative stress generation.

Applications

This study suggests that children should avoid ambient NO_2 exposure to decrease risks of asthma phenotypes, specifically those with *GSTP1* Val alleles.

Peer-review

The article clearly demonstrates the interaction between genetics (genetic polymorphism) and the environment (level of NO_2) in the development of asthma.

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