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NEW STUDY

Traffic, asthma and genetics: combining international birth cohort data to examine genetics as a mediator of traffic-related air pollution's impact on childhood asthma

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Abstract Associations between traffic-related air pollution and incident childhood asthma can be strengthened by analysis of gene-environment interactions, but studies have typically been limited by lack of study power. We combined data from six birth cohorts on: asthma, eczema and allergic rhinitis to 7/8 years, and candidate genes. Individual-level assessment of traffic-related air pollution exposure was estimated using land use regression or dispersion modeling. A total of 11,760 children were included in the Traffic, Asthma and Genetics (TAG) Study; 6.3 % reported physician-diagnosed asthma at school-age, 16.0 % had asthma at anytime during childhood, 14.1 % had allergic rhinitis at school-age, 10.0 % had eczema at school-age and 33.1 % were sensitized to any allergen. For *GSTP1* rs1138272, the prevalence of heterozygosity was 16 % (range amongst individual cohorts, 11–17 %) and homozygosity for the minor allele was 1 % (0–2 %). For *GSTP1* rs1695, the prevalence of heterozygosity was 45 % (40–48 %) and homozygosity for the minor allele, 12 % (10–12 %). For *TNF* rs1800629, the prevalence of heterozygosity was 29 % (25–32 %) and homozygosity for the minor allele, 3 % (1–3 %). TAG comprises a rich database, the largest of its kind, for investigating the effect of genotype on the association between air pollution and childhood allergic disease.

Keywords Air pollution · GSTP1 · TNF · Asthma · Wheeze · Gene-environment

This study was conducted for the TAG Study Group

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Abbreviations

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 East and West Germany plus the influence of traffic emissions and genetics study
LUR	Land-use regression
NO_2	Nitrogen dioxide
O_3	Ozone
PIAMA	Prevention and Incidence of asthma and mite allergy
$PM_{2.5}$	Particulate matter of diameter less than 2.5 μm
SAGE	Study of asthma, genes, and environment
TAG	Traffic, asthma and genetics study
TNF	Tumour necrosis factor
TLR	Toll-like receptor
TRAP	Traffic-related air pollution

Introduction

Traffic-related air pollution (TRAP) has been consistently associated with exacerbation of childhood asthma [1] and growing evidence supports an association with incident childhood asthma [2–5].

As part of the traffic related air pollution and childhood asthma (TRAPCA) international collaboration, individual estimates of air pollution exposure were assigned to children in four European birth cohorts [6, 7]. Using similar methodology, individual exposures were also assigned to children in two Canadian birth cohorts [8, 9]. To date, four of these cohorts have reported statistically significant associations between traffic-related air pollution and asthma or atopic disease during childhood [10–13]; and one has reported associations between TRAP and wheeze [14].

Gene-environment studies are of special interest in the examination of childhood asthma because they are able to identify children most susceptible to the harmful effects of TRAP [2, 15] and identification of these interactions could provide biological plausibility for epidemiologic observations. Oxidative stress genes are of particular interest [16] but there have been limited studies that have examined the development of asthma. Carriers of a specific *GSTP1* variant have been identified as a susceptible population in the association between TRAP and allergic sensitization [17], persistent wheeze [18], and asthma [19]. A common limitation in gene-environment studies is lack of sufficient power. To address this issue, and to improve our understanding of gene-environment interactions, investigators have called for analyses that combine data from studies with similar assessments of air pollution and asthma [20].

The Traffic, Asthma and Genetics study (TAG) has combined data from multiple birth cohorts to examine the influence of candidate genes related to oxidative stress and inflammation on the association between TRAP and the incidence of asthma, allergic rhinitis, eczema and wheeze in childhood. Here we describe the methodology used to

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pool data and provide information on the combined dataset and individual cohorts.

Methods

We included six birth cohort studies in TAG (Table 1): The Canadian Asthma Primary Prevention Study (CAPPS) [10], The Study of Asthma, Genetics and Environment (SAGE) [21], The Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE) [14, 17, 22], The German Infant Study on the Influence of Nutrition Intervention plus Environmental and Genetic Influences on Allergy Development Study (GINIplus) [23], the Influence of Life Style Factors on the Development of the Immune System and Allergies in East and West Germany plus the Influence of Traffic Emissions and Genetics Study (LISAplus) [23], and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study [24]. Detailed information for all six cohorts including case definitions are provided in the Supplementary Material. Children were born during the mid-to-late 1990s and recruitment was done primarily through hospitals, clinics and outpatient practices. SAGE identified children born in 1995 from a healthcare registry and asthma and allergy phenotypes were diagnosed by a physician at age 8, at which time parent histories were recalled retrospectively. CAPPS is the only study that did not originally recruit a population-based sample. Although SAGE and BAMSE recruited population-based samples, the data available for TAG are based on nested case–control samples.

In each cohort the following information was available for all or a subset of children: TRAP, assigned individually based on address at birth; assessment of physician-diagnosed asthma at 7 or 8 years; and available genotyping data for single nucleotide polymorphisms (SNPs) of primary interest. The studies recruited children primarily in urban areas. A primary objective of each study was examination of the epidemiology of childhood asthma. In CAPPS, GINI and PIAMA a portion of the population was assigned to a preventive intervention (education and counseling, promotion of hypoallergenic formula, and the use of dust mite-impermeable mattress covers).

Exposure assessment

For all cohorts except BAMSE, annual average NO_2, as an indicator of TRAP, was estimated for each child's birth address using land use regression models [6, 8, 9, 25]. For all study sites, integrated 14-day samples ($N_{total} = 40–116$) were collected. Potential predictors of traffic were screened by examining their correlation with measured air pollution and final models were assessed based on the coefficient of determination and root mean square error from cross-validation.

Models developed for the PIAMA cohort and for LISA and GINI children born in Munich were based on measurements collected between March 1999 and July 2000 [6]. The remaining LISA and GINI cities of Wesel and Leipzig were sampled in 2003 [26]. The model developed for CAPPS children born in Vancouver was based on measurements in the spring and fall of 2003 [9]; and the model developed for SAGE and CAPPS children born in Winnipeg was based on measurements in 2007 [8].

NO_2 estimates for the BAMSE birth cohort were assigned to birth addresses using dispersion models [14, 27]; emission data for traffic-generated NO_x were collected for the years 1990 and 2000. Pollutant dispersion was estimated using a dilution model based on wind speed, direction and precipitation [14]. Final models were validated using measurements taken outside the homes of 487 study children in the BAMSE cohort.

Ozone estimates were assigned to the European cohorts based on models developed in the APMoSPHERE project [28]. Predictions were made for the year 2001. In Canada, ozone estimates were assigned based on the average concentration among the three closest ambient monitors (within 50 km) using an inverse distance weighted approach.

Data transfer and creating a common database

Primary (asthma, wheeze) and secondary (allergic rhinitis, eczema, sensitization) outcome variables were available for all cohorts along with several potential confounders. Data were collected at different time points across the cohorts (Fig. 1), and there were slight differences in questionnaire wording and case definitions (see Supplementary Material). New TAG variables were derived from data common to all cohorts.

For all cohorts, questions pertaining to physician-diagnosed asthma, allergic rhinitis and eczema were asked when the child was 8 years of age, with the exception of CAPPS (assessed at 7 years).

Asthma at any time during follow-up ('ever') and wheeze 'ever' variables were created using every available follow-up to the age of 8 years. If parents reported no asthma or wheeze at every follow-up and no more than one follow-up had missing data then children were coded as not having ever asthma/wheeze. Children in the referent group missing data for more than two follow-up periods were excluded.

Sensitization was assessed by skin prick testing at age 7 for CAPPS and SAGE and by RAST at age 6 for GINI and LISA and at age 8 for BAMSE and PIAMA (defined as any specific IgE antibody value of 0.35 kU/L or greater). Results are presented for outdoor (birch, dactylis, timothy grass, mugwort, ragweed, rye, trees, and weeds) and indoor

Table 1 Summary of TAG birth cohorts

	Location	Study type	Cohort recruitment				Follow-up and cohort retention	
			Strategy	Dates	Target population	Number[a]	Age	Number[b]
CAPPS	Winnipeg & Vancouver, Canada	Birth cohort with asthma intervention	Prenatal clinics	1995	Pregnant women	545	7 years	380
SAGE	Manitoba, Canada	Population based birth cohort with nested asthma case–control	Provincial healthcare registry	1995	Newborns	723 in nested case–control	8 years	683
BAMSE	Stockholm, Sweden	Population based birth cohort with nested wheeze case–control	Initial Child Health visits	1994–1996	Newborns	982 in nested case–control	8 years	982
GINI	Munich & Wesel, Germany	Population based birth cohort with nutrition intervention	Maternity hospitals	1995–1998	Pregnant women	5,991	8 years (asthma); 6 years (wheeze)	3,241; 3,855
LISA	Munich, Wesel, Bad Honnef & Leipzig, Germany	Population based birth cohort	Obstetrical clinics	1997–1999	Pregnant women	3,095	8 years (asthma); 6 years (wheeze)	1,711; 2,577
PIAMA	The Netherlands	Population based birth cohort with mattress cover intervention	Midwife practices	1996–1997	Pregnant women	3,963	8 years	3,254

[a] Number of children included in the TAG database

[b] Number of children with complete follow-up in the TAG database

(alternaria, cats, cladosporium, dogs, feathers, house dust mites, molds, and cockroaches) allergens.

Results

There are a total of 15,134 children in the merged dataset (11,760 with complete follow-up; Table 1): 11,720 children have complete data on wheeze, 10,202 children have complete data on asthma and 10,743 children have assigned NO_2. NO_2 was the only traffic pollutant available for every cohort. In the SAGE, GINI and LISA studies, NO_2 was available only for children living in the urban centers of Winnipeg (SAGE) and Munich (GINI/LISA).

GSTP1 rs1138272 was available for 40 % of the combined dataset (21–94 % coverage by cohort), *GSTP1* rs1695 was available for 44 % (30–97 %) and *TNF* rs1800629 for 39 % (20–93 %). Additional SNPs of interest for allergic rhinitis and eczema were available for 11.4–38.9 % of the combined dataset and coverage within each cohort ranged from 1.9 to 94.9 % (Table 2).

The proportion of children with asthma, wheeze, allergic rhinitis, sensitization and eczema are shown in Table 3. The Canadian and Swedish studies had the highest incidence and prevalence of asthma while the German and Dutch cohorts had the lowest. This is due in part to study design, since CAPPS recruited only high-risk children and the data used for SAGE and BAMSE were from nested case–control studies. The proportion of children with physician-diagnosed asthma reported at 7/8 years was 6.3 % and ranged from 2.4 % in LISA to 31.4 % in SAGE. The proportion of children with a physician-diagnosis of asthma 'ever' was 16.0 % and ranged from 6.1 % in LISA to 41.6 % in CAPPS. The proportion of children with 'wheeze ever' was 44.5 % and ranged from 37.2 % in GINI to 62.6 % in SAGE. Finally, the proportion of children with both physician-diagnosed asthma ever and wheeze at 6/7/8 years was 7.2 % and ranged from 3.7 % in PIAMA to 43.7 % in SAGE. Overall, 1,412 (14.1 %) children reported allergic rhinitis and 2,083 (30.5 %) were sensitized to at least one aeroallergen. Among those reporting a doctor diagnosis of allergic rhinitis with available information on sensitization, 63.3 % (655/1,035) were sensitized to at least one aeroallergen. A breakdown of important covariates by cohort is provided in Tables 3 and 4.

NO_2 distributions for Germany and The Netherlands were similar while those for Canada (SAGE) and Sweden indicate slightly lower mean concentrations (Table 4). For NO_2 there was little overlap in concentration range

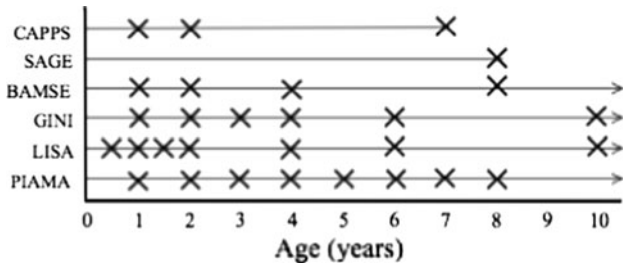

Fig. 1 Follow-up time points for each cohort

between SAGE and the other cohorts. The within-cohort variation for NO_2 in CAPPS and BAMSE was greater than the between-cohort variation (see Supplementary Material). In Canada, the within-cohort variation was due to the minimal overlap in the NO_2 concentrations between the two centers of Vancouver (18.9–55.2 μg/m^3) and Winnipeg (4.1–21.5 μg/m^3).

Table 5 reports genotype frequencies for the pooled data and by cohort. For *GSTP1* rs1138272, *GSTP1* rs1695 and *TNF* rs1800629, heterozygous and minor alleles were more common in PIAMA and major alleles were more common in CAPPS. Allele frequencies for additional SNPs of interest for allergic rhinitis and eczema are also included in Table 5.

Discussion

TAG represents the first consortium to examine the interaction between candidate genes of oxidative stress and inflammation, and traffic-related air pollution in relation to incident childhood airway diseases. Our database provides an unprecedented opportunity for pooled analysis of a significantly larger sample than in previously published analyses. This also allows novel analyses examining the interaction between air pollution and genome-wide data, which have also been integrated into the TAG database.

Based on the literature, and availability of genotyping within each cohort, we obtained data on three SNPs postulated to modify the relationship between air pollution and asthma: rs1138272/1799811 (*GSTP1*), rs1695/947894 (*GSTP1*) and rs1800629 (*TNF*). Mutations in the glutathione S-transferase (GST) enzymes have been associated with asthma. The activity of GST in the lung is influenced by the *GSTP1* enzyme [29] and this oxidative stress-modifying enzyme has been found to alter the response to air pollutants [30, 31]. Moreover, the *GSTP1* rs1695 SNP may have a differential effect on the development of asthma according to age—an association has been found for early onset of disease but not for late onset [15]. *TNF* responds to inflammation markers and has been shown to modify the relationship between ozone and asthma [31].

NO_2 is the pollutant with the most comprehensive coverage across the birth cohorts and is useful as a marker of within-city variability in exposure to traffic-related air pollutant. NO_2 is a reasonable indicator of TRAP and has been a useful exposure marker in previous epidemiological investigations [11, 32, 33].

Traffic-related air pollution exposures were calculated as annual averages for the home address reported at birth,

Table 2 Numbers and proportion of children with air pollution, birthweight and genotyping data

	Pooled		CAPPS[a]		SAGE		BAMSE		GINI		LISA		PIAMA	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Assigned NO_2	10,742	71.2	371	97.6	235	34.4	980	99.8	3,497	58.4	1,706	55.1	3,953	99.7
Assigned $PM_{2.5}$	5,893	39.0	185	48.7	–	–	–	–	1,083	18.1	672	21.7	3,953	99.7
Assigned $PM_{2.5}$ absorbance	8,615	57.1	185	48.7	–	–	–	–	3,497	58.3	980	31.7	3,953	99.7
Assigned O_3	11,757	77.9	186	48.9	–	–	–	–	5,283	88.2	2,351	76.0	3,937	99.3
Birthweight	13,670	90.3	380	100	670	98.1	976	99.4	4,636	77.4	3,094	99.9	3,914	98.8
GSTP1 rs1138272	6,100	40.3	352	92.6	543	79.4	923	94.0	1,308	21.8	1,006	32.5	1,968	49.7
GSTP1 rs1695	6,600	43.7	353	92.9	536	78.3	956	97.4	1,803	30.1	1,003	32.4	1,949	49.1
GSTP1 rs4891	4,355	28.8	–	–	–	–	932	94.9	1,432	23.9	–	–	1,991	50.2
TNF rs1800629	5,891	38.9	354	93.2	545	79.6	914	93.1	1,223	20.4	907	29.3	1,948	49.2
TLR2 rs1898830	1,864	12.3	354	93.2	581	80.4	–	–	–	–	–	–	929	23.4
TLR2 rs4696480	1,731	11.4	–	–	–	–	–	–	113	1.9	669	21.6	949	23.9
TLR4 rs10759931	3,062	20.2	–	–	–	–	–	–	1,226	20.5	906	29.3	930	23.5
TLR4 rs10759932	1,762	11.4	–	–	–	–	–	–	112	1.9	668	21.6	946	23.9
TLR4 rs1927911	4,012	26.5	355	93.4	580	80.2	–	–	1,226	20.5	904	29.2	947	23.9
TLR4 rs2737190	3,089	20.4	–	–	–	–	–	–	1,225	20.4	906	29.3	958	24.2
Total Number	15,134	–	380	–	683	–	982	–	5,991	–	3,095	–	3,963	–

[a] NO_2 was the only air pollutant modeled for the study city of Winnipeg

Table 3 Data on key variables, for pooled TAG data and by cohort (percentages are relative to the total children for given cohort within TAG)

	Pooled		CAPPS		SAGE		BAMSE		GINI		LISA		PIAMA	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Potential outcomes														
Physician-diagnosed asthma at 7/8 years	643	6.3	71	18.7	212	31.4	113	12.3	91	2.8	40	2.4	116	3.6
Physician-diagnosed asthma 'ever'	1,581	16.0	158	41.6	212	31.4	295	30.0	272	9.5	98	6.1	546	16.2
Physician-diagnosed asthma 'ever' AND parent reported wheeze at 6/7/8 years	668	7.2	70	18.4	172	43.7	125	13.6	122	4.3	61	3.9	118	3.7
Parent-reported wheeze at 6/7/8 years	1,265	11.5	87	22.9	249	62.6	165	18.0	341	8.9	208	9.5	215	6.6
Parent-reported wheeze 'ever'	5,209	44.5	178	46.8	249	62.6	578	58.9	1,432	37.2	1,115	43.3	1,657	47.0
Allergic rhinitis at 7/8 years	1,412	14.1	113	29.7	174	33.2	164	17.9	242	7.5	105	6.1	614	18.9
Sensitization to any allergen	2,264	33.1	167	45.5	201	29.6	235	30.6	634	32.3	323	27.1	704	37.7
Sensitization to any aeroallergen	2,083	30.5	165	45.0	189	27.9	158	20.6	574	29.3	300	25.3	697	37.3
Sensitization to any indoor aeroallergen	1,571	23.5	134	36.5	127	18.7	158	20.6	380	19.4	189	15.9	583	34.0
Sensitization to any outdoor aeroallergen	1,170	19.3	80	21.9	125	18.4	–	–	420	21.4	220	18.5	325	17.4
Physician-diagnosed eczema (2nd year)	1,673	13.8	43	11.5	–	–	207	21.1	467	10.9	336	12.3	620	16.7
Physician-diagnosed eczema (8th year; 7th year for CAPPS)	957	10.0	49	12.9	144	25.0	96	10.8	141	4.4	59	3.5	517	16.0
Additional covariates														
Intervention arm	3,235	21.4	202	53.2	–	–	–	–	2,252	37.6	–	–	781	19.7
Male gender	7,589	50.8	203	53.4	380	55.6	522	53.2	2,991	51.3	1,585	51.2	1,908	48.2
Maternal age at time of birth														
15–19 years	298	2.0	6	1.6	124	17.2	1	0.1	68	1.3	39	1.3	60	1.5
20–29 years	5,737	37.9	112	29.5	311	43.0	386	39.9	2,222	37.1	1,064	34.4	1,642	41.4
30–39 years	8,767	57.9	247	65.0	275	38.0	568	57.8	3,558	59.4	1,896	61.3	2,223	56.1
40–46 years	333	2.2	15	4.0	13	1.8	27	2.8	144	2.4	96	3.0	38	1.0
Parental history														
Maternal asthma	1,039	10.2	162	42.6	158	24.0	117	12.1	466	7.8	195	6.4	–	–
Maternal/paternal allergic disease	323	33.2	–	–	–	–	323	33.2	–	–	–	–	–	–
Maternal allergies	5,199	34.5	292	76.8	290	44.1	349	35.5	845	14.2	390	12.7	1,237	31.2
Paternal asthma	810	8.3	130	35.3	87	16.6	93	9.6	352	5.9	148	5.1	–	–
Paternal allergies	3,349	22.9	243	65.7	203	38.7	342	35.3	473	8.0	233	8.1	1,217	30.8
Place of birth														
Vancouver, Canada	186	1.2	186	49.0	–	–	–	–	–	–	–	–	–	–
Winnipeg, Canada	917	6.1	194	51.0	723	100	–	–	–	–	–	–	–	–
Stockholm, Sweden	284	1.9	–	–	–	–	284	29.0	–	–	–	–	–	–
Jarfalla, Sweden	313	2.1	–	–	–	–	313	32.0	–	–	–	–	–	–
Solna, Sweden	242	1.6	–	–	–	–	242	24.7	–	–	–	–	–	–
Sundbyberg, Sweden	140	0.9	–	–	–	–	140	14.3	–	–	–	–	–	–
Munich, Germany	4,414	29.2	–	–	–	–	–	–	2,949	49.2	1,465	47.3	–	–
Leipzig, Germany	976	6.5	–	–	–	–	–	–	–	–	976	31.5	–	–
Bad Honnef, Germany	306	2.0	–	–	–	–	–	–	–	–	306	9.9	–	–
Wesel, Germany	3,390	22.4	–	–	–	–	–	–	3,042	50.8	348	11.2	–	–
Groningen, The Netherlands	1,231	8.2	–	–	–	–	–	–	–	–	–	–	1,231	31.1
Rivm, The Netherlands	1,031	6.8	–	–	–	–	–	–	–	–	–	–	1,031	26.0
Wageningen, The Netherlands	555	3.7	–	–	–	–	–	–	–	–	–	–	555	14.0
Rotterdam, The Netherlands	1,146	7.6	–	–	–	–	–	–	–	–	–	–	1,146	28.9
Maternal smoking during pregnancy	2,702	20.2	29	7.7	131	18.1	138	14.1	739	15.4	536	18.0	1,129	22.9
Environmental tobacco smoke in the home														
1st year of life	2,600	32.5	74	19.5	–	–	185	18.9	1,323	27.8	758	26.7	1,583	41.5
2nd year of life	3,354	27.6	74	19.5	–	–	184	18.8	1,230	28.4	812	29.6	1,054	28.2
7th year of life	1,747	20.1	68	17.9	–	–	–	–	793	24.4	245	14.4	641	19.1
8th year of life	1,895	19.4	–	–	182	27.5	162	17.7	766	23.6	237	14.0	548	16.8

Table 4 Summary statistics for birthweight and each pollutant, by study

Metric	Units	Pooled		CAPPS		SAGE		BAMSE		GINI		LISA		PIAMA	
		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Birthweight	Grams	3,480 (509)	670–5,910	3,496 (642)	1,000–5,200	3,379 (636)	684–5,910	3,500 (574)	940–5,230	3,472 (465)	2,050–5,600	3,473 (445)	2,500–5,190	3,507 (546)	670–5,705
NO_2	$\mu g/m^3$	24.0 (7.4)	2.1–66.9	22.3 (11.5)	4.1–55.2	12.5 (3.3)	4.1–21.2	16.8 (9.2)	2.2–54.4	25.2 (4.6)	13.9–66.9	24.1 (5.6)	17.8–64.4	25.5 (7.7)	12.6–58.4
$PM_{2.5}$	$\mu g/m^3$	15.5 (3.0)	0.0–25.2	5.7 (2.6)	0.0–10.0	NA	NA	NA	NA	13.4 (1.3)	11.9–21.9	13.4 (1.3)	12.0–21.9	16.9 (2.0)	13.5–25.2
$PM_{2.5}$ absorbance	$\mu g/m^3$	1.7 (0.4)	0.0–5.0	1.6 (1.2)	0.0–5.0	NA	NA	NA	NA	1.7 (0.2)	0.8–4.3	1.7 (0.3)	1.2–4.4	1.7 (0.4)	0.8–3.7
O_3	$\mu g/m^3$	39.2 (6.9)	13.3–59.7	21.3 (2.9)	13.5–27.0	NA	NA	NA	NA	42.0 (5.4)	32.3–59.7	43.6 (4.6)	32.3–59.3	33.7 (4.7)	13.3–47.7

Pollutant data are calculated as annual averages based on the home address reported at birth

NO_2 data are based on traffic-related air pollution land use regression models for all cohorts except BAMSE where NO_2 is based on dispersion modeling

$PM_{2.5}$ and $PM_{2.5}$ absorbance data are based on traffic-related air pollution land use regression models. O_3 data are based on an atmosphere model

SD standard deviation, *NA* data not currently available

even though the measurements used to estimate TRAP were taken after birth for each of the cohorts. Recent findings [34–36] suggest that it is reasonable to apply a land use regression model from one time point to other time points up to 7 years into the past, because the spatial distribution of these pollutants is generally stable over time.

The availability of individual data from each cohort allows for pooled data analysis within TAG. There is adequate variability across birth cohorts, and cities, in air pollution distributions, and the prevalence of asthma and SNP frequency to facilitate epidemiologic analyses. The higher prevalence of asthma within CAPPS (high-risk cohort), SAGE (nested asthma case–control) and BAMSE (nested wheeze case–control) provides additional power for pooled analysis [37] but the inclusion of cohorts with differing study designs warrant cautious interpretation of pooled estimates. For CAPPS and BAMSE, the within-cohort variation in NO_2 is greater than the between-cohort variation, and supports the rationale for a pooled analysis versus a meta-analysis by cohort.

The main strength of TAG is the increased study power gained by combining data from multiple cohorts. However, this merging of data also carries some inherent limitations. While outcome and exposure variables across the European cohorts are comparable [38] the nonstandard definitions used for some potential confounder definitions may reduce precision of our estimates. A small number of potential confounders could not be included in our pooled dataset (mode of delivery, breastfeeding, parity, gas stove, visible mold and pets in the home) because it was not possible to harmonize data across each cohort. Asthma is defined as parent report of physician diagnosis in the European cohorts but is defined by a physical exam with a pediatric allergist in the Canadian cohorts. All pooled analyses will be replicated within each cohort to assess agreement between effect estimates [37]. This is another important strength of TAG because the consistency of effects across different populations can be examined using standardized methods. Further, children excluded from the pooled analysis due to insufficient air pollution data may have been more likely to live in rural areas, particularly within the SAGE cohort, and restricting to those with school age follow-up may have also resulted in selection bias.

These cohorts are unique in that they have highly detailed exposure assessment for TRAP and have recruited pregnant women or newborns and therefore have the ability to assess the development of asthma from birth. TAG comprises a rich database, the largest of its kind, for investigating the effect of genotype on the association between air pollution and childhood allergic disease.

Table 5 Genotype frequencies by cohort

	Pooled		CAPPS		SAGE		BAMSE		GINI		LISA		PIAMA	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
GSTP1 rs1138272[a]														
CC	5,079	83.3	304	86.4	481	88.6	774	83.9	1,083	82.8	818	81.3	1,619	82.3
CT	971	15.9	48	13.6	61	11.2	134	14.5	219	16.7	176	17.5	333	16.9
TT	50	1.0	0	–	1	0.2	15	1.6	6	0.5	12	1.2	16	0.8
GSTP1 rs1695[a]														
AA	2,835	43.0	172	48.7	260	48.5	434	45.4	752	41.7	435	43.4	782	40.1
AG	2,999	45.4	141	39.9	222	41.4	414	43.3	835	46.3	453	45.2	934	47.9
GG	766	11.6	40	11.3	54	10.1	108	11.3	216	12.0	115	11.5	233	12.0
GSTP1 rs4891														
TT	1,571	36.1	–	–	–	–	472	50.6	309	21.6	–	–	790	39.7
CT	2,176	50.0	–	–	–	–	352	37.8	886	61.9	–	–	938	47.1
CC	608	13.9	–	–	–	–	108	11.6	237	16.6	–	–	263	13.2
TNF rs1800629[a]														
GG	4,050	68.7	258	72.9	395	72.5	649	71.0	837	68.4	641	70.7	1,270	65.2
AG	1,686	28.6	92	26.0	136	25.0	245	26.8	348	28.5	250	27.5	615	31.6
AA	155	2.6	4	1.1	14	2.6	20	2.2	38	3.1	16	1.8	63	3.2
TLR2 rs1898830														
AA	753	40.4	141	39.8	227	39.1	–	–	–	–	–	–	385	41.4
AG	842	45.2	166	46.9	252	43.4	–	–	–	–	–	–	424	45.6
GG	269	14.4	47	13.3	102	17.6	–	–	–	–	–	–	120	12.9
TLR2 rs4696480														
AA	416	24.0	–	–	–	–	–	–	27	23.9	166	24.8	223	23.5
AT	855	49.4	–	–	–	–	–	–	55	48.7	355	53.1	445	46.9
TT	460	26.6	–	–	–	–	–	–	31	27.4	148	22.1	281	29.6
TLR4 rs10759931														
GG	1,162	37.9	–	–	–	–	–	–	494	40.3	319	35.2	349	37.5
GA	1,413	46.1	–	–	–	–	–	–	555	45.3	451	49.8	407	43.8
AA	487	15.9	–	–	–	–	–	–	177	14.4	136	15.0	174	18.7
TLR4 rs10759932														
TT	1,318	76.4	–	–	–	–	–	–	83	74.1	504	75.5	731	77.3
CT	380	22.0	–	–	–	–	–	–	26	23.2	150	22.5	204	21.6
CC	28	1.6	–	–	–	–	–	–	3	2.7	14	2.1	11	1.2
TLR4 rs1927911														
CC	2,249	54.8	193	54.4	323	55.7	–	–	666	54.3	516	57.1	551	58.2
TC	1,510	36.8	136	38.3	223	38.5	–	–	480	39.2	334	37.0	337	35.6
TT	253	6.2	26	7.3	34	5.9	–	–	80	6.5	54	6.0	59	6.2
TLR4 rs2737190														
AA	1,416	45.8	–	–	–	–	–	–	547	44.7	422	46.6	447	46.7
AG	1,360	44.0	–	–	–	–	–	–	555	45.3	397	43.8	408	42.6
GG	313	10.1	–	–	–	–	–	–	123	10.4	87	9.6	103	10.8

[a] Primary SNPs of interest for asthma

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