

Genome-wide interaction analysis of air pollution exposure and childhood asthma with functional follow-up

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ONLINE DATA SUPPLEMENT

1 STUDY SAMPLE DESCRIPTION

2 **BAMSE:** The Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE) is a
3 population based prospective birth cohort study with follow-up through the age of 16.(E1)
4 Between February 1994 and November 1996 newborns were recruited at their first child health
5 visit in predefined areas of Stockholm, Sweden (n=4,089). Infants were excluded if their family
6 was planning to move during the first year of life, an older sibling was already enrolled, serious
7 illness during the neonatal period or parents had insufficient knowledge of Swedish. Parental
8 questionnaires were used to assess physician diagnosed asthma, allergic rhinitis and eczema; and
9 episodes of wheezing at ages 1, 2, 4, 8, 12 and 16 years. At 8 and 16 years of age, all children of
10 the BAMSE study were invited to a clinical examination, and blood samples were obtained from
11 2,480 children and 2,547 children respectively. At 8 years DNA was extracted from 2,033
12 samples after exclusion of samples with too little blood, lack of questionnaire data, or if parental
13 consent to genetic analysis of the sample was not obtained. From these samples, all children with
14 a doctor's diagnosis of asthma (at any time during follow-up until 8 years of age) were selected
15 as cases (n=273) and children with no history of asthma or other allergic diseases were selected
16 as controls (n=273). After Quality Control (QC) a total of 238 cases (asthma ever) and 246
17 controls were retained in the GWAS analyses.(E2) Gene expression data (16 y) was available
18 from a subset of 263 individuals included in the MeDALL study.(E3) The study was approved
19 by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden. **Conflicts of interest:**
20 None. **Acknowledgements:** We would like thank all the families for their participation in the
21 BAMSE study. In addition, we would like to thank Eva Hallner, André Lauber and Sara Nilsson
22 at the BAMSE office for invaluable support.

GINI and LISA: 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 (LISApplus) Study is a population based birth cohort study. A total of 3097 healthy, full-term neonates were recruited between 1997 and 1999 in Munich, Leipzig, Wesel and Bad Honnef. The participants were not pre-selected based on family history of allergic diseases.(E4) A total of 5991 mothers and their newborns were recruited into the German Infant study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINIplus) between September 1995 and June 1998 in Munich and Wesel. Infants with at least one allergic parent and/or sibling were allocated to the interventional study arm investigating the effect of different hydrolysed formulas for allergy prevention in the first year of life.(E5) All children without a family history of allergic diseases and children whose parents did not give consent for the intervention were allocated to the non-interventional arm. Detailed descriptions of the LISApplus and GINIplus studies have been published elsewhere.(E4, 5) Information on ever having physician-diagnosed asthma and wheeze was collected using self-administered questionnaires completed by the parents. The questionnaires were completed at 6, 12, 18 and 24 months and 4, 6, 10 years of age in the LISApplus study and 1, 2, 3, 4, 6 and 10 years in the GINIplus study asking for each year of age since the previous follow-up and for wheeze in the past 12 months at age 10 years. DNA was collected at the age 6 and 10 years. For both studies, approval by the local Ethics Committees and written consent from participant's families were obtained. **Conflicts of interest:** None. **Acknowledgements:** The authors thank all the families for their participation in the GINIplus and LISApplus studies. Furthermore, we thank all members of the GINIplus and LISApplus Study Groups for their excellent work. The LISApplus Study Group consists of the following: Helmholtz Zentrum Muenchen - German Research Center for

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Environment and Health, Institute of Epidemiology I, Neuherberg (Heinrich J, Wichmann HE, Sausenthaler S, Chen C-M); University of Leipzig, Department of Pediatrics (Borte M), Department of Environmental Medicine and Hygiene (Herbarth O); Department of Pediatrics, Marien-Hospital, Wesel (von Berg A); Bad Honnef (Schaaf B); UFZ-Centre for Environmental Research Leipzig-Halle, Department of Environmental Immunology (Lehmann I); IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf (Krämer U); Department of Pediatrics, Technical University, Munich (Bauer CP, Hoffman U). The GINIplus Study Group consists of the following: Helmholtz Zentrum Muenchen - German Research Center for Environmental Health, Institute of Epidemiology I, Munich (Heinrich J, Wichmann HE, Sausenthaler S, Chen C-M, Thiering E, Tiesler C, Standl M, Schnappinger M, Rzehak P); Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A, Beckmann C, Groß I); Department of Pediatrics, Ludwig Maximilians University, Munich (Koletzko S, Reinhardt D, Krauss-Etschmann S); Department of Pediatrics, Technical University, Munich (Bauer CP, Brockow I, Grübl A, Hoffmann U); IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf (Krämer U, Link E, Cramer C); Centre for Allergy and Environment, Technical University, Munich (Behrendt H).

PIAMA: the Prevention and Incidence of Asthma and Mite Allergy study (PIAMA) is a birth cohort study consisting of two parts: a placebo controlled intervention study in which the effect of mite impermeable mattress covers on the development of asthma and allergy was studied and a natural history study in which no intervention took place. Details of the study design have been published previously.(E6) Recruitment took place in 1996-1997 through prenatal clinics. A screening questionnaire was distributed to pregnant women visiting one of 52 prenatal clinics at

three regions in the Netherlands. A total of 10,232 pregnant women completed a validated screening questionnaire. Mothers reporting a history of asthma, current hay fever or allergy to pets or house dust mite were defined as allergic. Based on this screening, 7,862 women were invited to participate, of whom 4,146 women (1,327 allergic and 2,819 non-allergic) gave written informed consent. Follow-up of the children took place at 3 months of age and yearly from 1 to 8 years of age. The Medical Ethical Committees of the participating institutes approved the study, and all participants gave written informed consent. Cases were defined as a parental report of doctor's diagnosed asthma at any time between age 1 – 8 y, controls were defined a report of a negative response to this question. **Conflicts of interest:** None. **Acknowledgement:** The PIAMA birth cohort study is a collaboration of the Institute for Risk Assessment Sciences, University Utrecht (B. Brunekreef), Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (H.A. Smit), Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven (A.H. Wijga), Department of Pediatrics, Division of Respiratory Medicine, Erasmus MC -Sophia, Rotterdam (J.C. de Jongste), Pulmonology (D.S. Postma) and Pediatric Pulmonology and Pediatric Allergology (G.H. Koppelman) of the University Medical Center Groningen and the Department of Immunopathology, Sanquin Research, Amsterdam (R.C. Aalberse), The Netherlands. The study team gratefully acknowledges the participants in the PIAMA birth cohort study, and all coworkers who helped conducting the medical examinations, field work and data management.

CHS: The Children's Health Study (CHS) is a longitudinal study of childhood asthma and other respiratory outcomes. It comprises of several cohorts with recruitment periods spanning from 1994 to 2003 and age at baseline ranging from age 5 to 14 years.(E7) The children were recruited

93 from 16 southern California communities. A genome-wide association study (GWAS) was
94 conducted based on a case-control sample of Hispanic White (HW) and non-Hispanic White
95 (NHW) children drawn from the CHS. Stratified random sampling was used to match the
96 controls with cases and was based on cohort, ethnicity, sex and follow up time that was
97 frequency matched. Cases had doctor-diagnosis of asthma at study entry (as reported by their
98 parent of guardian) or during follow-up to 2007. Study samples obtained from the buccal cells
99 were genotyped for over 550,000 single nucleotide polymorphisms (SNPs) spanning the genome
100 using the Illumina HumanHap550. After quality control of genotype data, such as only retaining
101 SNPs with call rate $\geq 95\%$, 3,000 subjects were available for analysis of which 1602 were non-
102 Hispanic whites (959 controls, 643 cases) with a baseline age ranging from 5 to 14 years.
103 Ancestry covariates were obtained from the software STRUCTURE. These latter covariates were
104 based on 557 ancestrally informative markers and quantified proportions of Caucasian, Native
105 American, Asian and African American ancestry for each individual. The regional air pollution
106 measurements were obtained from the central monitoring sites, which measured the air pollutants
107 continuously in each of the 16 study communities. Annual average values were computed for
108 analysis purposes. Logistic regression analysis was used to examine the interaction of NO_2 with
109 each SNP. The model included asthma as the outcome variable and the independent variables
110 included sex, age at baseline, community of residence, baseline environmental tobacco smoke
111 obtained from questionnaires filled by the parents, ancestry factors, SNP, NO_2 , and the
112 interaction of the SNP with NO_2 . **Conflicts of interest:** None.

113
114 **CAPPS and SAGE:** The Canadian Asthma Primary Prevention Study (CAPPS) is a prospective,
115 randomized controlled study with follow-up to the age of 7 years. 545 high-risk infants (those

116 having one first-degree relative with asthma or two first-degree relatives with other IgE mediated
117 diseases) were randomized prior to birth in the study centers of Vancouver and Winnipeg,
118 Canada. The multifaceted intervention included education and counseling on the risk factors of
119 asthma, specifically dust mite and environmental tobacco smoke avoidance, and breastfeeding
120 support. Parents completed questionnaires on respiratory symptoms and physician diagnoses at
121 1, 2 and 7 years. At 7 years children were examined by a pediatric allergist blinded to
122 intervention status and questionnaire responses; and peripheral blood was obtained from children
123 and their parents. In this study, asthma at age 7 years was defined from the pediatric allergist's
124 clinical exam.(E8),(E9) The Study of Asthma, Genetics and Environment (SAGE) is a
125 population-based birth cohort. Children were identified for inclusion from a provincial healthcare
126 registry. The study included all 13,980 children born in the province of Manitoba in 1995 with
127 continued residence in the province through 2002. Surveys were sent to each family when
128 children were 7 years old and, from the 3,598 responders, 723 children were selected for a nested
129 case-control study of asthma (246 asthmatics; 477 controls). Only these children were included
130 in the TAG collaboration, and are thus included in the current study. At mean age of 9 years,
131 children were examined by a pediatric allergist for allergic diseases, including asthma, and
132 symptoms.(E10) **Conflicts of interest:** None. **Acknowledgements:** We acknowledge Denise
133 Daley and the AllerGen Genetics team for assistance with CAPPS and SAGE data management
134 and transfer.

135 **METHODS**

136 **Air pollution assessment**

137 Measurements of NO₂ levels were obtained from ad hoc monitoring sites selected in each study
138 area, chosen to present the spatial distribution of air pollution levels relevant to the cohort
139 addresses, thus including regional background, urban background and traffic sites.
140 Measurements were performed at each site 3 times during 2 weeks in the cold, warm, and
141 intermediate seasons, and the results were used to estimate the annual average, adjusting for
142 temporal variation by using a centrally located background reference site. Linear models for
143 exposure assessment at any given site within a study area were developed using geographic
144 information system (GIS) data of land use and road traffic characteristics. The air pollution
145 exposure levels at birth were estimated by assigning the LUR estimated concentrations to the
146 children's home addresses at the time of birth. LUR modeling was also used to estimate
147 individual levels of traffic related air pollution in BAMSE at 16 years of age based on addresses
148 at the 16-years follow-up for the analyses of associations between NO₂ exposure and gene
149 expression levels.

150

151 **Asthma definitions**

152 In the European birth cohorts (BAMSE, GINI, LISA and PIAMA), asthma was defined as
153 physician diagnosed asthma reported at any time during follow up until 8 years of age
154 (approximately) and was obtained by parental questionnaires. Non-asthmatics were those never
155 having reported a doctor's diagnosis of asthma. In CHS, asthma was defined as physician
156 diagnosed asthma at baseline (1994-2003, age range 5-14 years) or at any time during the follow

up (until 2007) and was obtained by parental questionnaire or by self-report of the child at the time of their annual follow up pulmonary function test. In CAPPS, asthma was defined as a diagnosis at 7 years of age at a clinical examination by a pediatric allergist who was blinded to intervention status and questionnaire responses. In SAGE, asthma was defined as a parental report of doctor diagnosis which was confirmed by a pediatric allergist at 8 years of age. For further details see Table E2.

Genotyping and quality control

DNA was extracted from peripheral blood leucocytes. BAMSE, PIAMA, CAPPS and SAGE samples were genotyped using the Illumina Human610-Quad BeadChip (Illumina Inc, San Diego, CA, USA, <http://www.illumina.com>) and the genotyping has been described elsewhere.(E2) GINIplus and LISApplus samples were genotyped using Affymetrix Genome-wide Human SNP array 5.0 (Affymetrix, Santa Clara, CA, USA, <http://www.affymetrix.com>).(E16)

For CHS, DNA was extracted from buccal cells. Samples were genotyped using the Illumina HumanHap550, HumanHap550-Duo or Human610-Quad BeadChip microarrays.(E17)

SNPxNO₂ interaction and asthma; Discovery phase and meta-analysis

SNPs with minor allele frequency (MAF) < 0.05 and imputation quality score (R square for MACH users or INFO for IMPUTE users) < 0.3 were excluded before the meta-analysis step. P-values for each SNPxNO₂ across studies (taking sample size and direction of effect into account) were combined for the three studies, using METAL, version 2011-03-25.(E18) R version 3.0.2(E19) was used to generate the Manhattan plots and Quantile-Quantile plots (QQ-plot). The

QQ-plot was used to assess the distribution of SNP p-values and their deviation of observed associations versus expected under the null hypothesis of no association.(E20) Linkage disequilibrium (LD) between SNPs was calculated using SNAP(E21) and is based on HapMap Release 22 data using the CEU Population panel.

Adjustments for pre-defined potential confounders were made at the individual cohort level (before meta-analysis). Adjustment factors, defined using the literature, were age at last follow-up, sex, city or region where the child lived at birth (not adjusted for in GINI and LISA because only children from Munich were included), any environmental tobacco smoke exposure during the first year of life (parental report at year 1 questionnaire), and principal components for within European diversity assessed through genotype data (not adjusted for in GINI/LISA). All children included in the final analyses had a full set of confounders available. Table E1 describes data for cases and controls with a full set of confounders.

With an estimated interaction odds ratio of 1.2, equivalent to a similar range of interaction odds ratio of Glutathione S-transferase pi 1 gene (*GSTP1*) and traffic air pollution exposure in relation to childhood asthma,(E22) the sample size needed to gain 80% power is around 1,500.(E23) Logistic regression analyses for estimation of SNP main effect and NO₂ main effect on asthma was performed in using the same set of adjustment factors. Same procedure of meta-analysis as for the GWIS was applied to the SNP main effect analyses. NO₂ main effect was meta-analyzed for BAMSE, GINI/LISA and PIAMA using random effect model in STATA v13.1.

The two-step interaction approach

In step one, we tested separately in BAMSE, GINI/LISA and PIAMA the hypothesis of $H_0: \beta_{SNP} = 0$ using NO_2 as outcome in a combined set of cases and controls,(E24) which is an expansion of the traditional GxE interaction test using a case-only design. Meta-analysis of step one p-values was performed in METAL. A subset of SNPs that exceeded a meta-analysis $p < 0.05$ for the test in step one was further analyzed separately in BAMSE, GINI/LISA and PIAMA and then meta-analyzed in step two. It has been demonstrated that this two-step approach, an easily implemented method, is more powerful than a standard interaction test for most parameter settings.(E24)

The two degree of freedom (2df) test

Using the 2 df test we jointly tested the SNP main and $SNP \times NO_2$ interaction effects in BAMSE, GINI/LISA and PIAMA separately.(E25) A Wald test statistics, that follows a chi-squared distribution with 2 df under the $H_0: \beta_{SNP} = \beta_{SNP \times NO_2} = 0$, was constructed based on β_{SNP} and $\beta_{SNP \times NO_2}$ estimates and their corresponding 2x2 covariance matrix. The p-values from the separate cohorts were meta-analyzed in R version 3.0.2 using Fisher's method.

SNP \times NO₂ interaction and asthma; look-up

Adjustment factors were similar to those in the discovery phase, with the exception of environmental tobacco smoke exposure which was at 8 years of age in SAGE, no ancestry variables were adjusted for in CAPPS and SAGE, and region (community) which was not adjusted for in CHS. SNPs with $MAF < 0.05$ and imputation quality score ≤ 0.99 for CAPPS and SAGE, were excluded.

Direction of interaction effect and asthma risk was investigated by logistic regression analysis of NO₂ exposure on asthma, with stratification by genotype using dominant coding, adjusting for the same factors as in the SNPxNO₂ analysis.

eQTL analysis in lung tissue

Genotyping was carried out using the Illumina Human1M-Duo BeadChip and whole-genome expression profiling with an Affymetrix custom array (see GEO platform GPL10379, <http://www.ncbi.nlm.nih.gov/geo/>). All genes located within 500 kb of the top SNPs were selected. Imputed SNP data were used. Institutional Review Board ethical approval was obtained at the three sites, and all subjects provided written informed consent.

Gene expression analyses in peripheral blood cells

RNA from 16-year-old BAMSE subjects was extracted from PAXgene tubes (PAXgen Blood RNA Kit, Qiagen) with high quality standards, processed into biotin-labelled single-strand complementary DNA (sscDNA) according to manufacturer instructions of the WT Plus Reagent Kit and hybridized on Affymetrix Human Transcriptome Array 2.0 Genechips (HTA 2.0) for fluorometric intensity detection.(E26) Experimental design including randomization of samples into batches at crucial steps offered an efficient tracking and management of batch-related variation and afferent experimental variables. Assessment of purified molecules yield and quality (RIN(E27, 28)) was performed with state-of-the-art spectrophotometry (Trinean DropSense 96) and lab-on-a-chip microfluidic technologies (Agilent Tapestation), respectively, to ensure a robust normalization of inputs. Quality control of the gene expression data confirmed high

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quality with metrics beyond required thresholds. The dataset includes 45 samples from a pilot phase and 224 samples from an extended phase. Quality assessment was satisfying for 263 samples in total.(E26)

Data analysis was based on the space signal transformation robust multiarray average (SST-RMA) algorithm(E29) which combines Guanine Cytosine Count Normalization (GCCN) and Signal Space Transformation (SST) approaches, first normalizing intensities based on the probe affinity difference associated with GC content, then ‘stretching’ the intensity distribution by decompressing the Fold Change ratios with a power law mapping, prior to applying RMA algorithm (E30) with quantile normalization(E31). The Combat method(E32) was used to adjust for batch effect between pilot and extended phases. Linear regression was used to assess associations between NO₂ exposure and expression levels adjusting for age, sex and peripheral blood cell count.(E26)

DNA methylation analysis in the BAMSE cohort

In the BAMSE cohort epigenome-wide DNA methylation was measured in 472 Caucasian children, using DNA extracted from blood samples collected at the age of 8 years.(E26) An aliquot (500 ng) of DNA per sample underwent bisulfite conversion using the EZ-96 DNA Methylation kit (Zymo Research Corporation, Irvine, USA). Samples were plated onto 96-well plates in randomized order. Samples were processed with the Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc., San Diego, USA).

Quality control of analysed samples was performed using standardized criteria. Samples were excluded in case of sample call rate <99%, colour balance >3, low staining efficiency, poor

extension efficiency, poor hybridization performance, low stripping efficiency after extension and poor bisulfite conversion. We also applied multidimensional scaling (MDS) plot to evaluate gender outliers based on chromosome X data, that produced two separated clusters for male and female. We omitted 5 samples that do not belong to the distinct cluster. Furthermore, we applied median intensity plot for methylated and unmethylated intensity by using the minfi R package (3 samples below the 10.5 cutoff were excluded). All above led to exclusion of 8 samples.

Probes with a single nucleotide polymorphism in the single base extension site with a frequency of >5% were excluded, (E33) as were probes with non-optimal binding (non-mapping or mapping multiple times to either the normal or the bisulphite-converted genome), and the probe belonging to chromosome X and chromosome Y, resulting in the exclusion of 46,799 probes, leaving a total of 438,713 probes in the analysis. Furthermore, we implemented “DASEN” recommended from watermelon package to do signal correction and normalization.(E34)

Adjustment for cell type (estimated counts of CD8+ T cells, CD4+ T cells, NK cells, B cells, Monocytes and Granulocytes)(E35) was done using the minfi R package(E36) in the robust linear regression analysis between CpG site methylation and long-term NO₂ exposure at birth.

methQTL analyses in peripheral blood

The CpG sites investigated for association with long-term NO₂ exposure in BAMSE were also investigated for cis-methylation quantitative trait locus (cis-methQTL) effects (n=460) evaluating the eight SNPs significant in the look-up analyses. Adjustment was done for age, sex, environmental tobacco smoke exposure during first year of life, NO₂ exposure at birth, municipality, ever doctor’s diagnosis of asthma up to 8 years of age, cell type (estimated counts

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of CD8⁺ T cells, CD4⁺ T cells, NK cells, B cells, Monocytes and Granulocytes)(E35) using the minfi R package (E36) and batch (bisulfite treatment date). A SNP was considered a methQTL if it survived 5% FDR correction for multiple testing.

DNA methylation difference by short term diesel exposure

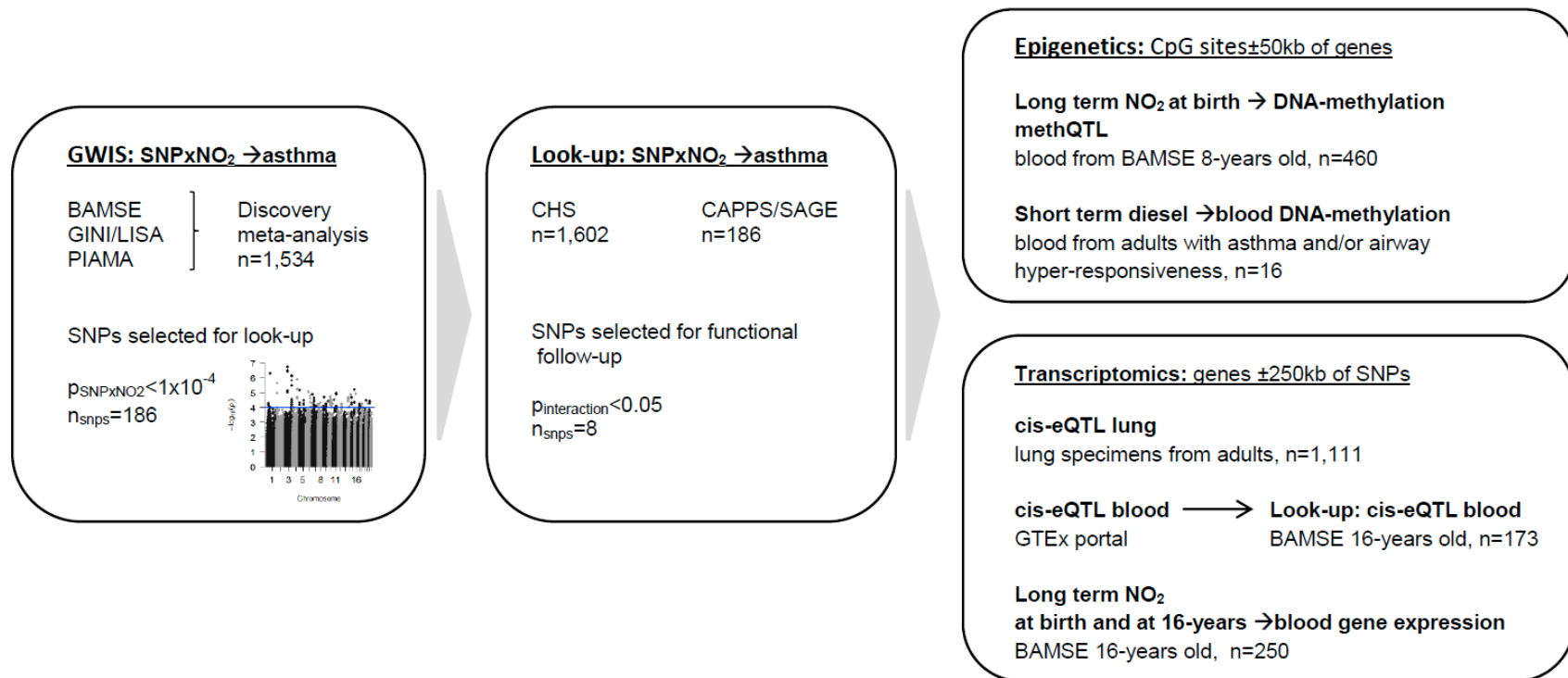
Exposure to diesel exhaust particles (DEP, nominally, 300 µg/m³ PM_{2.5}) and filtered air particles (FAP) for 2 hours on two separate occasions at least two weeks apart followed a randomized crossover design. The subjects alternated between light exercise (15 min) and rest (45 min) on a stationary bike during exposure. Peripheral blood mononuclear cells (PBMCs) were collected at baseline, 6 hours, and 30 hours post-exposure. Methylation was measured using the Illumina Infinium 450K bead chip methylation array (accession number GSE56553, <http://www.ncbi.nlm.nih.gov/geo/>). Linear mixed effects modeling were applied to the measurements to compare post-DEP vs. pre-DEP, and post-FAP vs. pre-FAP, assuming that changes are detectable at 6 hr and persist at 30 hr post-exposure (thus, it compared DE6hr&30hr against non-DE6hr&30hr). Hits were CpG sites demonstrating significant change for the DE comparison, but not for the FA comparison. Written consent was obtained from all subjects, and the protocol was approved by the institutional review board for human studies at the University of British Columbia.

FANTOM5 and the Human Protein Atlas

Gene expression was checked in different tissues according to the FANTOM5 data.(E37) Significant expression of *B4GALT5* is seen in most cells, including the lungs and airways,

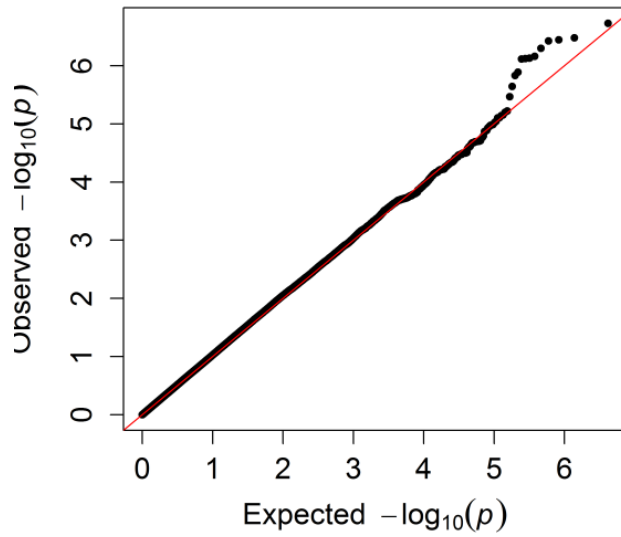
314 however it is specifically highly expressed in neutrophils and CD14 monocytes. *ADCY2* is highly
315 expressed in the brain, but importantly, also found at significant levels in the fetal and adult lung
316 and bronchi. *DLG2* expression is seen in most cells including neutrophils, regulatory T cells and
317 lung. The Human Protein Atlas(E38) was further used to identify protein expression in normal
318 respiratory system tissue and smooth muscle tissue. *ADCY2* was expressed at medium levels in
319 nasopharynx- and bronchial epithelial cells, lung macrophages and smooth muscle tissue (Table
320 E14 in the online data supplement). *DLG2* was expressed at low to medium levels, in
321 nasopharynx and bronchus. *B4GALT5* could not be evaluated for protein expression.

322 **Figure E1.** Overview of the study design. The procedure to identify new childhood asthma susceptibility loci that interact with traffic-
 323 related air pollution exposure. After GWIS discovery phase meta-analysis in three European cohorts, all SNPs with $p < 1 \times 10^{-4}$ for
 324 interaction were investigated for look-up evaluation in two separate North American cohorts. SNPs that were marginally significant in
 325 the look-up evaluation were further investigated in transcriptomics and epigenetics analyses.



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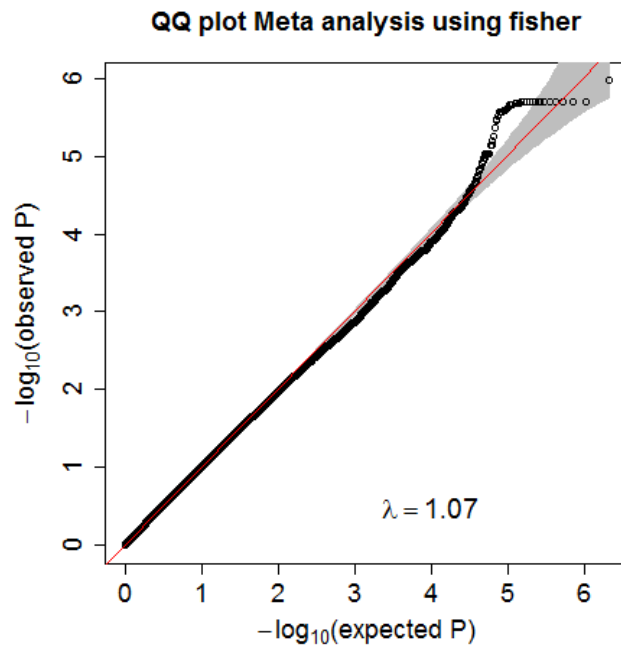
327 **Figure E2.** Quantile-quantile plot for the discovery genome-wide interaction meta-analysis of
328 the association between SNPxNO₂ interaction and asthma ($\lambda=1.03$).



329

330

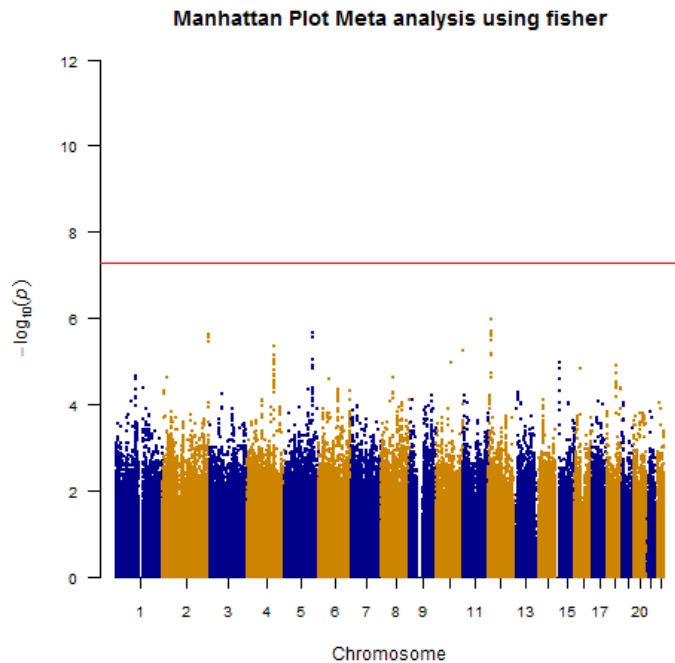
331 **Figure E3.** Quantile-quantile plot for the 2 df genome-wide meta-analysis ($\lambda=1.07$).



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333

334 **Figure E4.** Manhattan plot for the 2 df genome-wide meta-analysis. The horizontal red line
335 indicates the genome-wide significance threshold ($p < 1 \times 10^{-7}$).



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337

Figure E5. Gene expression levels of the *B4GALT5* gene in whole blood according to genotyping groups for SNP rs686237 (using an additive model) investigated in the GTEx Portal (n=338), $p=4.00 \times 10^{-4}$. The x-axis represents the three genotyping groups for SNP rs686237 with the number of subjects. Homo Ref: AA, Het:AC, Homo Alt: CC.

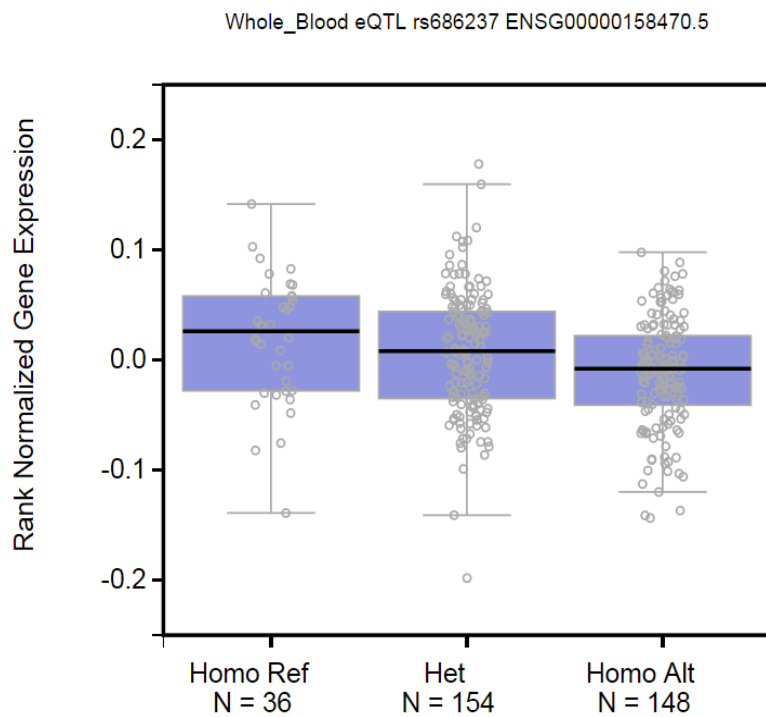
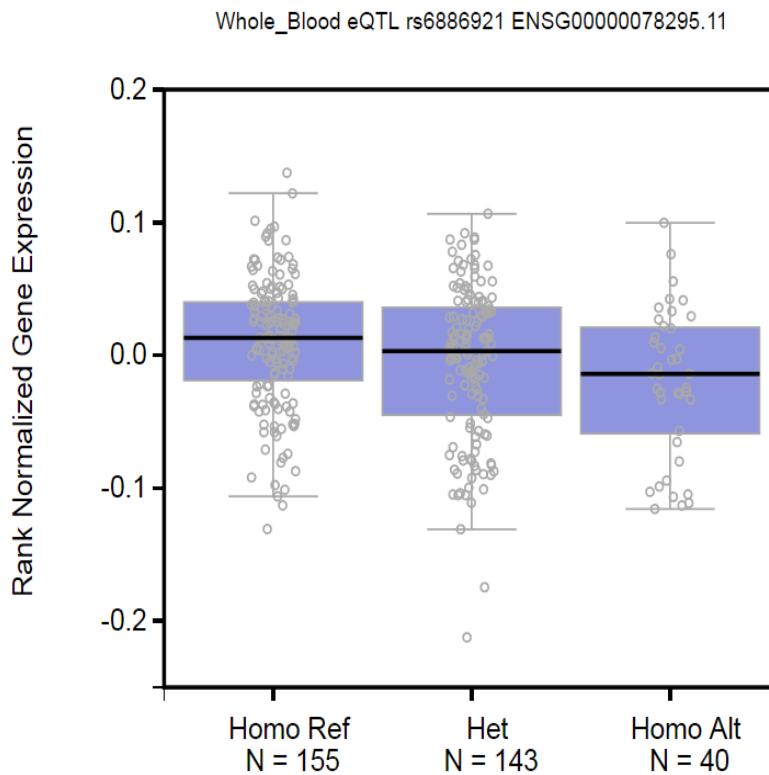


Figure E6. Gene expression levels of the *ADCY2* gene in whole blood according to genotyping groups for SNP rs6886921 (using an additive model) investigated in the GTEx Portal (n=338), $p=4.50 \times 10^{-4}$. The x-axis represents the three genotyping groups for SNP rs6886921 with the number of subjects. Homo Ref: CC, Het:CT, Homo Alt: TT.



351 **Table E1.** Characteristics of the children in the studied cohorts.

Discovery	Never		Total	Age at last follow-up		Tobacco smoke exposure* (%)	NO ₂ exposure levels (µg/m ³) mean/median (min-max/5 th -95 th percentile)
	Asthmatics	asthmatics		mean years (min-max)	Boys (%)		
							13.56 / 11.97
BAMSE	235	246	481	8.3 (7.4-10.5)	265 (55)	88 (18)	(6.0-31.8 / 7.6-23.1)
							21.6 / 20.6
GINI/LISA	64	661	725	10.2 (9.4-11.3)	390 (54)	127 (18)	(11.5-61.1 / 13.9-30.9)
							25.0 / 25.9
PIAMA	155	173	328	8.1 (7.8-9.6)	173 (53)	74 (23)	(12.6-54.6 / 14.0-37.9)
Discovery total	454	1,080	1,534				
Look-up	Never		Total	Age at last follow-up		Tobacco smoke exposure (%)	NO ₂ exposure levels (µg/m ³) mean/median (min-max/5 th -95 th percentile)
	Asthmatics	asthmatics		mean years (min-max)	Boys (%)		
							20.7 / 19.6
CHS	643	959	1,602	8.8 (5.2-14.3)	846 (53)	205 (13)	(4.2-40.8 / 4.6-38.0)
							15.4 / 13.4
CAPPS/SAGE	49	137	186	7.4 (7.0-8.0) [†]	106 (57)	40 (22) [‡]	(4.5-55.2 / 5.8-35.3)
Total	1,146	2,176	3,322				

352 * Any environmental tobacco smoke exposure during first year of life (parental reported at year 1 questionnaire). [†]7 years of age in
353 CAPPS, 8 years of age in SAGE. [‡]first year of life for CAPPS, year 8 for SAGE.

354 **Table E2.** Study characteristics genotyping and imputation procedure, traffic air pollution exposure assessment method, definitions
 355 and prevalence of outcomes, as well as statistical software used.

Discovery cohorts				Look-up cohorts	
Cohort characteristics	BAMSE	GINI/LISA	PIAMA	CHS	CAPPS/SAGE
Study design	Population based birth cohort.	Population based birth cohort (with nutrition intervention for GINI)	Population based birth cohort (with mattress cover intervention and allergic/non-allergic parents)	Stratified random sampling was used to match the controls with cases and was based on cohort, ethnicity, sex and follow-up time (frequency matched).	Birth cohort with asthma intervention (high risk infants)/ Population based birth cohort
Age at enrolment	Newborns	Pregnant women	Pregnant women	Ranging from age 5-14yrs with a mean of 9 years	Pregnant women/ Newborns
Population source (area)	Stockholm, Sweden	Munich, Wesel/ Munich, Wesel, Bad Honnef and Leipzig, Germany	Greater Groningen, Bilthoven, Wageningen and surroundings and greater Rotterdam, Netherlands	Southern California	Vancouver and Winnipeg, Canada/ Manitoba, Canada
Enrolment period	1994-1996	1995-1998/1997-1999	1996-1997	1993, 1996, 2003	1995

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Cohort recruitment	Community population register	Maternity hospitals/ Obstetrical clinics	Midwife practices	From 16 school communities (3 separate cohorts)	Parental clinics/Provincial health care registry.
Total number of recruited children	4,089	5,991/3,097	4,146	~12,000, 3,000 in GWAS, 1,788 non-Hispanic white in GWAS	549/16,320
Follow-up time points (year of life)	1,2,4,8,12,16	1,2,3,4,6,10/0.5,1,1.5,2,4,6,10	1,2,3,4,5,6,7,8	Annual from age 10 to 18 in 1993 and 1996 cohorts, annual from age 5 to 17 in 2003 cohort	1,2,7/8
Assessment of outcome and covariates	Parental reported by questionnaires	Parental reported by questionnaires	Parental reported by questionnaires	Parental reported by questionnaire	Parental reported by questionnaires and confirmation of diagnoses by pediatric allergist
Phenotype definitions					
Asthma cases	Ever having a doctor's diagnosed asthma up to age 8 years. Parental questionnaire assessing	Ever having a doctor's diagnosed asthma up to age 10. Parental questionnaire assessing physician diagnosed asthma.	Ever having a doctor's diagnosed asthma up to age 8. Parental questionnaire assessing physician diagnosed asthma.	Ever having a doctor's diagnosis as of 2007, based on parental or child report.	Asthma diagnosis at 7 years of age at the clinical examination by a pediatric allergist. /Asthma diagnosis at 8 years of age. Parent report of physician

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	physician diagnosed asthma.				diagnosed asthma, confirmed by pediatric allergist.
Healthy controls	Never having a doctor's diagnosed asthma or allergic disease up to age 8	Never having a doctor's diagnosed asthma up to age 10	Never having a doctor's diagnosed asthma up to age 8	Never having a doctor's diagnosed of asthma as of 2007	No asthma diagnosis at 7 years of age./ No asthma diagnosis at 8 years of age
Traffic air pollution					
Estimation model	LUR	LUR	LUR	Outdoor air pollution monitoring stations in each of the study communities	LUR
Time of measurements	For three two-week intervals October 2008 - April 2011	Munich, Augsburg and small nearby towns sampled for three two-week intervals October 2008-April 2011	For three two-week intervals October 2008 - April 2011	Continuous measurements from 1994 onward in each study community	Vancouver: Spring and fall 2003/ Winnipeg: 2007
Genotyping					
Criteria for selection of genotyping (GWAS)	Asthma case-control n=505	Children from Munich n=1,511	Asthma case-control n=404	Asthma case-control. Stratified random sampling was used to match the controls with cases and was based on cohort,	Asthma case-control n=956

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				ethnicity, sex and follow-up time (frequency matched) n=1,788	
Genotyping platform	Illumina 610-Quad BeadChip	Affymetrix 5.0	Illumina 610-Quad Beadchip	Illumina HumanHap550, HumanHap550-Duo or Human610-Quad BeadChip	Illumina 610-Quad BeadChip
Genetic Quality control before imputation					
SNP call rate threshold	97%	95%	95%	95%	95%
HWE p-value threshold	1×10^{-4} in controls	1×10^{-5}	1×10^{-4} in controls	1×10^{-5} in controls	1×10^{-4}
MAF threshold	5%	1%	1%	No exclusions for any of the look-up SNPs	1%
Other exclusion criteria	-	-	Ethnicity	-	SNPs with >2 Mendelian errors
Number of SNPs after filtering	515,695	357,125	516,527	172 (of 186 selected for look-up evaluation)	122 (of 186 selected for look-up evaluation)
Imputation					

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Imputation software	MACH	IMPUTE 2	IMPUTE V2	MACH	MACH
NCBI build	36	36	36	36	36
Reference panel	Hap Map release 22	Hap Map release 22	Hap Map release 22	HapMap release 22	Hap Map release 22
Number of SNPs after imputation	2,180,015	2,619,389	2,197,335	NA	NA
Inclusion criteria					
Ethnicity	Caucasian	Caucasian	Caucasian	Non-Hispanic white	Caucasian
Genotyping call rate threshold	97%	95%	95%	95%	97%
Other exclusion criteria	Twins or any multiple births	Heterozygosity thresholds: Mean ± 4 SD; sex discrepancies	Heterozygosity thresholds: Mean ± 4 SD; sex discrepancies	-	Heterozygosity thresholds: Mean ± 3 SD; samples had to pass gender and Mendelian transmission error checks; Twins or duplicate samples
Genotype-phenotype association software and version	ProbABELv0.1-3	ProbABEL v0.1-9e	ProbABEL v0.1-9e and R	SAS v9.4	STATA v13.1

Table E3. List of the top SNPs ($p < 1 \times 10^{-4}$, $n=186$) selected for look-up from the discovery phase genome-wide interaction meta-analysis of the association between SNP \times NO₂ interaction and asthma, ordered by chromosome location.

Chr	SNP	position	A1	A2	Nearest gene	Discovery GWIS meta-analysis p-value n=1,534	Heterogeneity p-value
1	rs2205722	20481895	A	C	<i>UBXN10,VWA5B1</i>	7.73×10^{-5}	0.8705
1	rs7515342	29652302	A	G	<i>PTPRU,MATN1</i>	5.32×10^{-5}	0.8765
1	rs7556278	29652615	C	T	<i>PTPRU,MATN1</i>	5.17×10^{-5}	0.8795
1	rs7547385	29652625	C	G	<i>PTPRU,MATN1</i>	7.22×10^{-5}	0.8736
1	rs7521309	29653160	C	T	<i>PTPRU,MATN1</i>	6.03×10^{-5}	0.8932
1	rs4654349	29653808	C	T	<i>PTPRU,MATN1</i>	5.91×10^{-5}	0.8206
1	rs4654350	29653811	C	G	<i>PTPRU,MATN1</i>	5.27×10^{-5}	0.8282
1	rs10518644	80652485	A	G	<i>LOC646526,LOC100129325</i>	5.05×10^{-7}	0.9592
1	rs12025147	80689103	A	C	<i>LOC646526,LOC100129325</i>	9.50×10^{-5}	0.8376
2	rs11096550	18722984	C	G	<i>NT5C1B,FLJ41481</i>	1.07×10^{-5}	0.2737
2	rs16985416	18729707	A	G	<i>NT5C1B,FLJ41481</i>	1.12×10^{-5}	0.2901
2	rs4614937	18731669	A	G	<i>NT5C1B,FLJ41481</i>	2.27×10^{-6}	0.0638
3	rs11718057	65069823	A	T	<i>LOC730057,MAGI1</i>	3.59×10^{-7}	0.9077
3	rs11706125	65069843	A	G	<i>LOC730057,MAGI1</i>	3.33×10^{-7}	0.9017
3	rs7651862	65069950	G	T	<i>LOC730057,MAGI1</i>	1.87×10^{-7}	0.8372
3	rs13066946	65070988	A	G	<i>LOC730057,MAGI1</i>	3.77×10^{-7}	0.9088
3	rs2371862	65074490	A	C	<i>LOC730057,MAGI1</i>	7.26×10^{-6}	0.7745
3	rs2170573	65074846	A	G	<i>LOC730057,MAGI1</i>	7.92×10^{-6}	0.7724
3	rs2128406	65075037	C	T	<i>LOC730057,MAGI1</i>	7.81×10^{-6}	0.7687
3	rs9873349	65079771	A	C	<i>LOC730057,MAGI1</i>	9.49×10^{-6}	0.7332
3	rs939441	181518859	C	T	<i>LOC647249,TTC14</i>	9.67×10^{-5}	0.7306
3	rs2878951	181526858	C	T	<i>LOC131054,TTC14</i>	2.60×10^{-5}	0.7011
3	rs1464358	181527268	C	T	<i>LOC131054,TTC14</i>	2.67×10^{-5}	0.6883
3	rs10937030	181527552	A	T	<i>LOC131054,TTC14</i>	9.81×10^{-5}	0.7349

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3	rs7431270	181529402	A	G	<i>LOC131054,TTC14</i>	3.42×10^{-5}	0.8498
3	rs1356909	181531444	G	T	<i>LOC131054,TTC14</i>	4.16×10^{-5}	0.8554
3	rs13325203	181533917	C	T	<i>LOC131054,TTC14</i>	4.45×10^{-5}	0.8565
3	rs9810983	181546287	C	T	<i>LOC131054,TTC14</i>	4.53×10^{-5}	0.8535
3	rs4854972	181550117	A	G	<i>LOC131054,TTC14</i>	4.60×10^{-5}	0.852
3	rs10937032	181550599	A	G	<i>LOC131054,TTC14</i>	8.88×10^{-5}	0.8702
3	rs1402227	181554680	G	T	<i>LOC131054,TTC14</i>	6.74×10^{-5}	0.8188
3	rs1464359	181556243	A	G	<i>LOC131054,TTC14</i>	6.95×10^{-5}	0.8216
3	rs9871421	181561017	A	C	<i>LOC131054,TTC14</i>	6.03×10^{-5}	0.9009
3	rs7634356	181630586	C	T	<i>LOC131054,TTC14</i>	7.68×10^{-7}	0.8948
3	rs1533700	181646575	A	T	<i>LOC131054,TTC14</i>	6.93×10^{-7}	0.8877
3	rs9823620	181654283	C	T	<i>LOC131054,TTC14</i>	1.48×10^{-6}	0.996
3	rs982698	181702681	C	T	<i>LOC131054,TTC14</i>	7.40×10^{-7}	0.8862
3	rs12497999	181767441	C	T	<i>LOC131054,TTC14</i>	7.54×10^{-7}	0.8861
3	rs12496529	181786971	A	C	<i>LOC131054,TTC14</i>	3.41×10^{-6}	0.9849
4	rs3910954	138821160	A	G	<i>PCDH18,LOC641365</i>	2.05×10^{-5}	0.2357
4	rs3843891	138828912	A	C	<i>PCDH18,LOC641365</i>	2.49×10^{-5}	0.2266
4	rs7672176	138913964	A	C	<i>PCDH18,LOC641365</i>	6.03×10^{-6}	0.1673
4	rs7670760	138936781	C	T	<i>PCDH18,LOC641365</i>	1.29×10^{-6}	0.1705
5	rs727432	7716078	G	T	<i>ADCY2</i>	6.67×10^{-5}	0.9545
5	rs4143882	7717364	A	G	<i>ADCY2</i>	4.75×10^{-5}	0.9406
5	rs6886921	7718539	C	T	<i>ADCY2</i>	7.03×10^{-6}	0.9787
5	rs4266448	116700966	G	T	<i>RPS17P2,LOC728342</i>	5.43×10^{-5}	0.6054
5	rs11749394	116708435	G	T	<i>RPS17P2,LOC728342</i>	5.47×10^{-5}	0.6058
5	rs10061651	116708519	A	C	<i>RPS17P2,LOC728342</i>	5.98×10^{-5}	0.6235
5	rs4457117	116708659	C	T	<i>RPS17P2,LOC728342</i>	6.00×10^{-5}	0.6271
5	rs4443456	116708696	C	T	<i>RPS17P2,LOC728342</i>	6.12×10^{-5}	0.6251
5	rs6595040	116708999	C	T	<i>RPS17P2,LOC728342</i>	6.17×10^{-5}	0.6255
5	rs4623185	116709042	A	G	<i>RPS17P2,LOC728342</i>	3.20×10^{-5}	0.6703
5	rs4448037	116709139	C	T	<i>RPS17P2,LOC728342</i>	6.70×10^{-5}	0.6216

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5	rs6860005	116709836	C	T	<i>RPS17P2,LOC728342</i>	6.20×10^{-5}	0.6257
5	rs4458619	116711165	C	T	<i>RPS17P2,LOC728342</i>	6.07×10^{-5}	0.6272
5	rs13159487	116711565	A	G	<i>RPS17P2,LOC728342</i>	6.01×10^{-5}	0.6281
5	rs10069843	116711962	A	G	<i>RPS17P2,LOC728342</i>	6.83×10^{-5}	0.6225
5	rs10039799	116712524	C	T	<i>RPS17P2,LOC728342</i>	6.90×10^{-5}	0.6229
5	rs4259204	116713920	A	G	<i>RPS17P2,LOC728342</i>	6.04×10^{-5}	0.63
5	rs4566827	116714196	A	G	<i>RPS17P2,LOC728342</i>	6.21×10^{-5}	0.6295
6	rs16895780	65560035	C	T	<i>LOC100130393,LOC727977</i>	9.03×10^{-6}	0.538
6	rs9489520	119187072	A	G	<i>C6orf204,ASF1A</i>	4.39×10^{-5}	0.9041
6	rs601575	119526519	C	G	<i>FAM184A,MAN1A1</i>	1.71×10^{-5}	0.5923
6	rs660682	119526898	A	G	<i>FAM184A,MAN1A1</i>	2.42×10^{-5}	0.5975
6	rs6916978	119539264	A	G	<i>MAN1A1</i>	1.61×10^{-5}	0.4681
6	rs2558	119542373	A	G	<i>MAN1A1</i>	9.59×10^{-5}	0.8643
6	rs12201119	162514036	A	G	<i>PARK2,PARK2</i>	5.19×10^{-5}	0.9753
6	rs9456749	162518420	A	G	<i>PARK2,PARK2</i>	5.07×10^{-5}	0.7625
6	rs12205861	162518803	C	T	<i>PARK2,PARK2</i>	1.00×10^{-4}	0.9644
6	rs12208027	162522787	C	G	<i>PARK2,PARK2</i>	9.22×10^{-5}	0.9099
6	rs9355987	162525256	C	T	<i>PARK2,PARK2</i>	9.73×10^{-5}	0.9271
7	rs1713918	2910713	A	C	<i>CARD11</i>	1.33×10^{-5}	0.4129
7	rs11765988	50385016	A	G	<i>LOC100132224,IKZF1</i>	2.27×10^{-5}	0.5979
7	rs7800411	50386119	C	T	<i>LOC100132224,IKZF1</i>	3.38×10^{-5}	0.6609
7	rs12719039	50386443	C	T	<i>LOC100132224,IKZF1</i>	3.89×10^{-5}	0.7561
7	rs3807552	50578236	A	G	<i>DDC</i>	7.13×10^{-5}	0.766
7	rs3829897	50597258	G	T	<i>DDC</i>	7.16×10^{-5}	0.1999
7	rs6593010	50597382	A	G	<i>DDC</i>	4.12×10^{-5}	0.3377
7	rs10278338	50597764	C	T	<i>DDC</i>	4.15×10^{-5}	0.3392
7	rs11489734	50603224	A	T	<i>DDC,GRB10</i>	6.45×10^{-5}	0.2824
7	rs11238214	50603512	A	G	<i>DDC,GRB10</i>	8.57×10^{-5}	0.2526
7	rs13228274	50603895	A	T	<i>DDC,GRB10</i>	8.64×10^{-5}	0.2528
7	rs1839740	50613774	C	T	<i>DDC,GRB10</i>	8.70×10^{-5}	0.2543

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7	rs12669770	50623828	A	G	<i>GRB10,GRB10,GRB10</i>	8.94×10^{-5}	0.2556
7	rs4245555	50628903	C	T	<i>GRB10,GRB10,GRB10</i>	7.37×10^{-5}	0.8823
7	rs884843	73083725	A	G	<i>ELN,ELN,ELN,ELN</i>	9.40×10^{-5}	0.8952
7	rs362726	102994470	C	T	<i>RELN</i>	8.07×10^{-5}	0.08233
7	rs13223489	136419075	C	T	<i>LOC100128744</i>	7.66×10^{-5}	0.1109
8	rs2945882	8159034	A	G	<i>FLJ10661,PRAGMIN</i>	6.13×10^{-5}	0.1633
8	rs2955551	8160844	A	G	<i>FLJ10661,PRAGMIN</i>	7.17×10^{-5}	0.1774
8	rs12681261	28495356	C	T	<i>FZD3,EXTL3</i>	6.77×10^{-5}	0.7136
8	rs164658	28497485	A	G	<i>FZD3,EXTL3</i>	6.32×10^{-5}	0.7467
8	rs17265947	63901079	A	G	<i>NKAIN3</i>	4.65×10^{-5}	0.8752
8	rs17336727	107438950	A	T	<i>LOC100128259,OXRI</i>	8.84×10^{-5}	0.6875
9	rs10812133	2490687	A	G	<i>SMARCA2,FLJ35024</i>	7.69×10^{-5}	0.8804
9	rs10491713	2496236	G	T	<i>SMARCA2,FLJ35024</i>	7.99×10^{-5}	0.9203
9	rs2383131	19892822	C	T	<i>SLC24A2,SMNP</i>	2.03×10^{-5}	0.3345
9	rs11142863	73325288	C	T	<i>TRPM3,TMEM2</i>	7.91×10^{-5}	0.1689
9	rs11142864	73325468	A	C	<i>TRPM3,TMEM2</i>	7.89×10^{-5}	0.1687
9	rs17056968	73345792	C	T	<i>TRPM3,TMEM2</i>	9.49×10^{-5}	0.1526
9	rs10869033	73355863	G	T	<i>TRPM3,TMEM2</i>	5.43×10^{-5}	0.1853
9	rs10781028	73358763	C	T	<i>TRPM3,TMEM2</i>	9.18×10^{-5}	0.1545
9	rs12685824	73361662	A	T	<i>TRPM3,TMEM2</i>	6.36×10^{-5}	0.1973
9	rs539215	128101333	A	C	<i>PBX3,FAM125B</i>	3.70×10^{-5}	0.8072
10	rs1194673	53811658	A	G	<i>DKK1,LOC644522</i>	7.45×10^{-5}	0.4049
10	rs1149776	53812481	A	G	<i>DKK1,LOC644522</i>	7.25×10^{-5}	0.4061
10	rs1149772	53815310	C	T	<i>DKK1,LOC644522</i>	6.12×10^{-5}	0.4151
10	rs1149769	53816103	C	G	<i>DKK1,LOC644522</i>	5.09×10^{-5}	0.4274
10	rs1194671	53817795	C	T	<i>DKK1,LOC644522</i>	4.57×10^{-5}	0.4334
10	rs1194670	53818050	A	C	<i>DKK1,LOC644522</i>	4.39×10^{-5}	0.4357
10	rs1194668	53818632	A	G	<i>DKK1,LOC644522</i>	3.11×10^{-5}	0.476
10	rs6480837	53819249	A	C	<i>DKK1,LOC399774</i>	3.87×10^{-5}	0.4431
10	rs1194664	53820821	C	T	<i>DKK1,LOC399774</i>	3.76×10^{-5}	0.4435

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10	rs1194662	53823021	C	T	<i>DKK1,LOC399774</i>	1.95×10^{-5}	0.5658
10	rs1194661	53823035	A	G	<i>DKK1,LOC399774</i>	2.00×10^{-5}	0.563
10	rs1194659	53823557	C	T	<i>LOC644522,LOC399774</i>	1.98×10^{-5}	0.5638
10	rs1660793	53827025	C	T	<i>LOC644522,LOC399774</i>	2.03×10^{-5}	0.565
10	rs1621210	53827070	C	T	<i>LOC644522,LOC399774</i>	1.78×10^{-5}	0.5786
10	rs1660792	53827231	A	C	<i>LOC644522,LOC399774</i>	2.00×10^{-5}	0.5664
10	rs1733704	53827622	C	T	<i>LOC644522,LOC399774</i>	2.02×10^{-5}	0.5661
10	rs1733706	53828582	A	G	<i>LOC644522,LOC399774</i>	2.10×10^{-5}	0.5737
10	rs12412762	81897450	C	T	<i>PLAC9,ANXA11</i>	4.88×10^{-5}	0.7776
10	rs17100316	81903317	A	G	<i>ANXA11,ANXA11</i>	4.72×10^{-5}	0.7723
10	rs12769764	81907093	C	G	<i>ANXA11,ANXA11</i>	3.19×10^{-5}	0.8254
10	rs3862518	81907937	C	T	<i>ANXA11,ANXA11</i>	3.43×10^{-5}	0.83
10	rs12268619	81910640	A	C	<i>ANXA11,ANXA11</i>	6.29×10^{-5}	0.5474
10	rs2304410	81911790	C	T	<i>ANXA11,ANXA11</i>	6.72×10^{-5}	0.5515
10	rs10466226	81914035	A	G	<i>ANXA11,ANXA11</i>	6.92×10^{-5}	0.5543
10	rs10466228	81914353	A	G	<i>ANXA11,ANXA11</i>	6.89×10^{-5}	0.5514
10	rs11201966	81921760	C	T	<i>ANXA11,ANXA11</i>	6.92×10^{-5}	0.557
10	rs11201972	81922660	C	T	<i>ANXA11,ANXA11</i>	6.98×10^{-5}	0.5565
10	rs12769115	81923481	A	G	<i>ANXA11,ANXA11</i>	8.62×10^{-5}	0.6426
10	rs12763392	81924975	C	T	<i>ANXA11,ANXA11</i>	6.37×10^{-5}	0.686
10	rs3851055	81928076	C	T	<i>ANXA11,ANXA11</i>	7.09×10^{-5}	0.6603
10	rs12256429	81928612	C	T	<i>ANXA11,ANXA11</i>	4.56×10^{-5}	0.7135
10	rs12779955	81930844	C	T	<i>ANXA11,ANXA11</i>	7.30×10^{-5}	0.6549
10	rs2244524	104476964	C	T	<i>SFXN2</i>	6.06×10^{-5}	0.3672
11	rs10834971	26337381	A	C	<i>TMEM16C</i>	3.12×10^{-5}	0.4219
11	rs1545863	83381380	G	T	<i>DLG2</i>	7.79×10^{-5}	0.875
11	rs1545864	83383163	C	G	<i>DLG2</i>	1.05×10^{-5}	0.9265
11	rs12418356	83385605	A	G	<i>DLG2</i>	1.03×10^{-5}	0.9283
11	rs1601091	83388136	C	T	<i>DLG2</i>	7.73×10^{-5}	0.8753
11	rs1384749	83397130	G	T	<i>DLG2</i>	8.15×10^{-5}	0.8673

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11	rs11233881	83409188	A	C	<i>DLG2</i>	1.29×10^{-5}	0.9346
11	rs963146	83423444	A	G	<i>DLG2</i>	8.61×10^{-5}	0.9208
11	rs1384751	83432571	A	C	<i>DLG2</i>	8.84×10^{-5}	0.9223
12	rs34577	95049250	A	G	<i>LOC100132930,ELK3</i>	8.18×10^{-5}	0.9316
12	rs34579	95050134	C	T	<i>LOC100132930,ELK3</i>	5.91×10^{-5}	0.6654
14	rs11157090	39421942	G	T	<i>FBXO33,LOC644919</i>	3.47×10^{-5}	0.9558
14	rs7158182	39423507	A	G	<i>FBXO33,LOC644919</i>	2.48×10^{-5}	0.9898
14	rs10150213	39423615	A	T	<i>FBXO33,LOC644919</i>	3.48×10^{-5}	0.9515
14	rs8004765	39424373	A	G	<i>FBXO33,LOC644919</i>	3.35×10^{-5}	0.9543
14	rs11844981	39429789	A	G	<i>FBXO33,LOC644919</i>	2.18×10^{-5}	0.9907
14	rs10151130	39441365	C	T	<i>FBXO33,LOC644919</i>	3.24×10^{-5}	0.9644
14	rs1957231	39442479	A	C	<i>FBXO33,LOC644919</i>	3.20×10^{-5}	0.9646
14	rs17180573	39443197	A	T	<i>FBXO33,LOC644919</i>	3.17×10^{-5}	0.9649
14	rs17180580	39443302	A	G	<i>FBXO33,LOC644919</i>	3.36×10^{-5}	0.9661
14	rs10149674	39443919	G	T	<i>FBXO33,LOC644919</i>	3.19×10^{-5}	0.9655
14	rs10137555	39444113	A	G	<i>FBXO33,LOC644919</i>	2.13×10^{-5}	0.9916
14	rs11847742	39447796	C	T	<i>FBXO33,LOC644919</i>	3.21×10^{-5}	0.9659
14	rs1957229	39448355	A	G	<i>FBXO33,LOC644919</i>	3.22×10^{-5}	0.9662
14	rs1957221	39464798	A	T	<i>FBXO33,LOC644919</i>	3.72×10^{-5}	0.9689
14	rs10144664	39465191	C	T	<i>FBXO33,LOC644919</i>	3.73×10^{-5}	0.9689
14	rs10150328	58450585	C	T	<i>LOC440181,AKR1B1P5</i>	8.24×10^{-5}	0.9966
14	rs4900108	91823837	A	C	<i>CPSF2,SLC24A4</i>	1.35×10^{-5}	0.9069
15	rs999842	20551713	A	G	<i>CYFIP1</i>	2.12×10^{-5}	0.6508
15	rs7179062	20553025	C	G	<i>CYFIP1</i>	4.85×10^{-5}	0.2729
15	rs7179447	20553224	C	G	<i>CYFIP1</i>	6.53×10^{-5}	0.2907
15	rs7182254	91715858	C	T	<i>UNQ9370,LOC283682</i>	6.33×10^{-6}	0.08291
15	rs1489135	91717789	A	T	<i>UNQ9370,LOC283682</i>	4.54×10^{-5}	0.03214
15	rs12439678	91718676	C	T	<i>UNQ9370,LOC283682</i>	4.81×10^{-5}	0.06388
16	rs237191	26580307	A	G	<i>HS3ST4,C16orf82</i>	1.18×10^{-5}	0.1072
17	rs4794298	47151791	A	G	<i>CA10,CA10</i>	6.10×10^{-5}	0.8789

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17	rs7223543	47156558	A	G	<i>CA10,CA10</i>	8.17×10^{-5}	0.8288
17	rs1917998	47160827	A	C	<i>CA10,CA10</i>	6.92×10^{-5}	0.9682
17	rs11869209	47163241	A	C	<i>CA10,CA10</i>	7.06×10^{-5}	0.9335
17	rs7214924	47165513	G	T	<i>CA10,CA10</i>	9.60×10^{-5}	0.9593
17	rs8074550	47168474	A	T	<i>CA10,CA10</i>	5.73×10^{-5}	0.9904
18	rs12455842	32096284	C	T	<i>MOCOS</i>	6.10×10^{-5}	0.8954
18	rs1057251	32102579	C	T	<i>MOCOS</i>	6.18×10^{-5}	0.8752
18	rs12457919	32108100	A	C	<i>MOCOS,FHOD3</i>	5.52×10^{-5}	0.871
19	rs2097982	62472846	A	G	<i>ZNF805,ZNF460</i>	3.35×10^{-5}	0.6119
20	rs686237	47804141	A	C	<i>B4GALT5,SLC9A8</i>	5.43×10^{-5}	0.5867
21	rs13046992	40221984	A	G	<i>PCP4,IGSF5,DSCAM</i>	3.81×10^{-5}	0.9652
21	rs2837308	40229327	A	G	<i>PCP4,DSCAM</i>	4.92×10^{-5}	0.7549

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Table E4. Top SNPs ($p < 1 \times 10^{-4}$) from the genome-wide interaction meta-analysis of association between SNP \times NO₂ and asthma, using the two-step approach.

								Discovery GWIS meta-analysis	Look-up	
								n=1,534	CHS n=1,602	CAPPS/ SAGE n=186
Chr	SNP	Position (build 37)	Minor Allele	Major Allele	MAF	Nearest gene	Feature	p-value*	p-value†	p-value†
3	rs7651862	65,094,910	T	G	0.48	<i>MAGII</i>	-	1.87×10^{-7}	0.77	NA
3	rs11706125	65,094,803	A	G	0.48	<i>MAGII</i>	-	3.33×10^{-7}	NA	NA
3	rs11718057	65,094,783	T	A	0.48	<i>MAGII</i>	-	3.59×10^{-7}	0.77	NA
3	rs13066946	65,095,948	A	G	0.48	<i>MAGII</i>	-	3.77×10^{-7}	0.76	NA
18	rs12457919	33,854,102	C	A	0.10	<i>MOCOS, FHOD3</i>	-	5.52×10^{-5}	0.017	NA
18	rs12455842	33,842,286	C	T	0.10	<i>MOCOS, ELP2, RNU4P3</i>	intron	6.10×10^{-5}	0.014	0.55
18	rs1057251	33,848,581	T	C	0.10	<i>MOCOS, RNU4P3, LOC791126</i>	missense	6.18×10^{-5}	0.013	0.58

Shown are top SNPs from the discovery phase, using the two-step approach, ordered by p-value. All p-values given are two-sided. Chr, chromosome; Minor Allele, according to discovery phase cohorts; MAF, minor allele frequency according to BAMSE; NA, SNP not available. *Genome-wide significance threshold $p < 4.18 \times 10^{-7}$, after Bonferroni correction of 119,521 SNPs that were tested in the second step of the two-step approach. †Significance threshold, $p < 0.05$.

367 **Table E5.** Top SNPs ($p < 1. \times 10^{-4}$) from the genome-wide interaction meta-analysis of association between SNP \times NO₂ and asthma,
 368 using the 2 df test

SNP	CHR	POS	Meta-analysis p-value	p-value BAMSE	p-value PIAMA	p-value GINI/LISA	Gene	ensembl_gene_id
rs3825270	12	13115294	1.08X10 ⁻⁶	9.13X10 ⁻⁶	5.10X10 ⁻³	1.15X10 ⁻¹	KIAA1467	ENSG00000084444
rs12424184	12	13113046	1.98X10 ⁻⁶	1.02X10 ⁻⁵	5.09X10 ⁻³	2.02X10 ⁻¹	KIAA1467	ENSG00000084444
rs1386004	12	13104726	2.00X10 ⁻⁶	1.01X10 ⁻⁵	5.07X10 ⁻³	2.09X10 ⁻¹	KIAA1467	ENSG00000084444
rs4763925	12	13110340	2.00X10 ⁻⁶	1.03X10 ⁻⁵	5.09X10 ⁻³	2.04X10 ⁻¹	KIAA1467	ENSG00000084444
rs3803097	12	13110639	2.00X10 ⁻⁶	1.03X10 ⁻⁵	5.09X10 ⁻³	2.04X10 ⁻¹	KIAA1467	ENSG00000084444
rs1552389	12	13091145	2.01X10 ⁻⁶	1.00X10 ⁻⁵	4.99X10 ⁻³	2.14X10 ⁻¹	KIAA1467	ENSG00000084444
rs1463623	12	13090515	2.01X10 ⁻⁶	1.00X10 ⁻⁵	4.99X10 ⁻³	2.14X10 ⁻¹	KIAA1467	ENSG00000084444
rs3741818	12	13105804	2.01X10 ⁻⁶	1.01X10 ⁻⁵	5.08X10 ⁻³	2.08X10 ⁻¹	KIAA1467	ENSG00000084444
rs3741817	12	13106058	2.01X10 ⁻⁶	1.01X10 ⁻⁵	5.09X10 ⁻³	2.08X10 ⁻¹	KIAA1467	ENSG00000084444
rs7956640	12	13094384	2.01X10 ⁻⁶	1.00X10 ⁻⁵	5.00X10 ⁻³	2.14X10 ⁻¹	KIAA1467	ENSG00000084444
rs7963271	12	13101279	2.01X10 ⁻⁶	1.00X10 ⁻⁵	5.04X10 ⁻³	2.12X10 ⁻¹	KIAA1467	ENSG00000084444
rs7303584	12	13097367	2.02X10 ⁻⁶	1.00X10 ⁻⁵	5.02X10 ⁻³	2.14X10 ⁻¹	KIAA1467	ENSG00000084444
rs4763923	12	13099175	2.02X10 ⁻⁶	1.00X10 ⁻⁵	5.03X10 ⁻³	2.14X10 ⁻¹	KIAA1467	ENSG00000084444
rs7956609	12	13094309	2.03X10 ⁻⁶	1.00X10 ⁻⁵	5.05X10 ⁻³	2.14X10 ⁻¹	KIAA1467	ENSG00000084444
rs4763920	12	13087757	2.05X10 ⁻⁶	1.03X10 ⁻⁵	5.00X10 ⁻³	2.14X10 ⁻¹	KIAA1467	ENSG00000255621
rs4077753	5	152175101	2.13X10 ⁻⁶	1.55X10 ⁻⁶	7.12X10 ⁻¹	1.03X10 ⁻²	LINC01470	ENSG00000249484
rs4077752	5	152175070	2.14X10 ⁻⁶	1.55X10 ⁻⁶	7.12X10 ⁻¹	1.04X10 ⁻²	LINC01470	ENSG00000249484
rs13168888	5	152171627	2.14X10 ⁻⁶	1.55X10 ⁻⁶	7.12X10 ⁻¹	1.04X10 ⁻²	LINC01470	ENSG00000249484

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rs4583879	5	152169871	2.19X10-6	1.55X10-6	7.31X10-1	1.04X10-2	LINC01470	ENSG00000249484
rs4763924	12	13099819	2.20X10-6	7.92X10-6	7.12X10-3	2.10X10-1	KIAA1467	ENSG00000084444
rs2741043	2	234232340	2.41X10-6	1.25X10-6	1.65X10-1	6.33X10-2	UGT1A10	ENSG00000242366
rs1377460	2	234201376	2.46X10-6	1.23X10-6	1.57X10-1	6.95X10-2	UGT1A8	ENSG00000242366
rs11055218	12	13103493	2.59X10-6	1.00X10-5	6.74X10-3	2.10X10-1	KIAA1467	ENSG00000084444
rs2924450	2	234229144	2.61X10-6	1.36X10-6	1.67X10-1	6.30X10-2	UGT1A10	ENSG00000242366
rs2741031	2	234203455	2.66X10-6	1.26X10-6	1.67X10-1	6.94X10-2	UGT1A8	ENSG00000242366
rs13183376	5	152188573	2.73X10-6	1.73X10-6	6.90X10-1	1.26X10-2	LINC01470	ENSG00000249484
rs11738913	5	152178685	2.76X10-6	1.55X10-6	7.13X10-1	1.38X10-2	LINC01470	ENSG00000249484
rs4763922	12	13092766	3.14X10-6	2.56X10-5	3.31X10-3	2.08X10-1	KIAA1467	ENSG00000084444
rs10492247	12	13091857	3.35X10-6	1.00X10-5	8.81X10-3	2.14X10-1	KIAA1467	ENSG00000084444
rs1817154	2	234225330	3.47X10-6	1.37X10-6	2.27X10-1	6.30X10-2	UGT1A10	ENSG00000242366
rs7670760	4	138936781	4.35X10-6	4.17X10-4	7.70X10-1	7.90X10-5		
rs1552682	10	133920710	5.59X10-6	6.03X10-7	1.62X10-1	3.45X10-1	KIAA1467	ENSG00000165752
rs9804722	12	13107528	6.43X10-6	8.03X10-5	3.08X10-3	1.59X10-1	KIAA1467	ENSG00000084444
rs1316824	12	13118808	7.08X10-6	1.38X10-4	4.40X10-3	7.25X10-2	KIAA1467	ENSG00000084444
rs2175071	4	138913175	7.18X10-6	1.58X10-2	9.31X10-1	3.02X10-6		
rs11737900	5	152168653	9.20X10-6	7.82X10-6	7.56X10-1	9.95X10-3	LINC01470	ENSG00000249484
rs7445606	5	152180302	9.26X10-6	1.08X10-6	7.45X10-1	7.36X10-2	LINC01470	ENSG00000249484
rs10034241	4	138934133	9.33X10-6	1.89X10-2	8.29X10-1	3.83X10-6		
rs1509265	4	138943226	9.35X10-6	1.90X10-2	8.32X10-1	3.80X10-6		
rs1568967	4	138932735	9.43X10-6	1.89X10-2	8.29X10-1	3.87X10-6		

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rs1509268	4	138931754	9.44X10-6	1.89X10-2	8.29X10-1	3.87X10-6		
rs999842	15	20551713	1.06X10-5	2.34X10-4	1.38X10-1	2.15X10-3	NIPA2	ENSG00000140157
rs12415107	10	71983648	1.08X10-5	2.87X10-7	2.99X10-1	8.20X10-1	PALD1	ENSG00000107719
rs3910954	4	138821160	1.15X10-5	4.28X10-2	4.83X10-1	3.68X10-6	LOC101927414	
rs1532896	18	51631900	1.22X10-5	2.14X10-6	1.57X10-1	2.41X10-1	LOC105372130	ENSG00000267172
rs4958581	5	152167922	1.24X10-5	2.40X10-5	6.69X10-1	5.12X10-3	LINC01470	ENSG00000249484
rs12517563	5	152188838	1.41X10-5	1.55X10-6	7.32X10-1	8.40X10-2	LINC01470	ENSG00000249484
rs237191	16	26580307	1.44X10-5	1.54X10-2	5.49X10-4	1.16X10-2		
rs7179062	15	20553025	1.47X10-5	2.83X10-4	2.48X10-1	1.43X10-3	NIPA2	ENSG00000140157
rs17213661	4	138950587	1.55X10-5	4.53X10-2	8.19X10-1	2.86X10-6	RP11-793B23.1	ENSG00000250034
rs9944650	18	51638460	1.80X10-5	3.32X10-6	1.57X10-1	2.41X10-1	LOC105372130	ENSG00000267172
rs7303887	12	13082442	1.82X10-5	1.97X10-4	7.11X10-3	9.10X10-2	RP11-377D9.3	ENSG00000255621
rs9319731	18	51646327	1.89X10-5	3.50X10-6	1.57X10-1	2.41X10-1		
rs1467032	4	138963335	1.95X10-5	4.05X10-2	8.10X10-1	4.19X10-6		
rs11166507	1	101002400	2.21X10-5	1.75X10-4	3.45X10-3	2.64X10-1		
rs11940232	4	138953336	2.23X10-5	4.62X10-2	8.17X10-1	4.24X10-6	RP11-793B23.1	ENSG00000250034
rs2978529	8	62281020	2.33X10-5	4.26X10-3	3.70X10-3	1.07X10-2	CLVS1	ENSG00000177182
rs4763321	12	13133937	2.39X10-5	6.27X10-5	6.97X10-2	3.97X10-2	KIAA1467	ENSG00000084444
rs6680442	1	100996734	2.42X10-5	2.31X10-4	3.74X10-3	2.03X10-1		
rs4614937	2	18731669	2.42X10-5	7.92X10-6	5.87X10-1	3.79X10-2		
rs9464379	6	56311633	2.48X10-5	3.60X10-4	7.69X10-2	6.55X10-3	COL21A1	ENSG00000124749
rs7554373	1	100998523	2.53X10-5	1.88X10-4	3.74X10-3	2.64X10-1		

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rs7179447	15	20553224	2.60X10-5	2.96X10-4	3.05X10-1	2.11X10-3	NIPA2	ENSG00000140157
rs7672176	4	138913964	2.67X10-5	5.91X10-3	8.99X10-1	3.71X10-5		
rs1526240	4	138860824	2.85X10-5	1.76X10-1	6.55X10-1	1.83X10-6	NIPA2	ENSG00000250777
rs6535922	4	138859507	2.86X10-5	1.76X10-1	6.54X10-1	1.84X10-6	NIPA2	ENSG00000250777
rs11151379	18	51665841	3.07X10-5	5.94X10-6	1.58X10-1	2.46X10-1		
rs11151377	18	51662188	3.10X10-5	6.11X10-6	1.57X10-1	2.43X10-1		
rs3849640	4	138839286	3.20X10-5	1.80X10-1	6.79X10-1	1.98X10-6	NIPA2	ENSG00000250777
rs1526241	4	138863957	3.27X10-5	1.77X10-1	6.60X10-1	2.13X10-6	NIPA2	ENSG00000250777
rs1553600	18	51665132	3.29X10-5	6.08X10-6	1.57X10-1	2.61X10-1		
rs1506630	18	51656338	3.30X10-5	6.14X10-6	1.57X10-1	2.60X10-1		
rs3843891	4	138828912	3.32X10-5	2.44X10-2	6.11X10-1	1.69X10-5	NIPA2	ENSG00000250777
rs1526228	4	138834660	3.32X10-5	2.34X10-1	7.60X10-1	1.42X10-6	NIPA2	ENSG00000250777
rs1526226	4	138905805	3.56X10-5	1.90X10-1	6.77X10-1	2.13X10-6		
rs12605156	18	51649112	3.85X10-5	7.87X10-6	1.57X10-1	2.41X10-1		
rs13170178	5	152189295	3.94X10-5	2.84X10-5	7.23X10-1	1.49X10-2	LINC01470	ENSG00000249484
rs9959500	18	51653994	4.02X10-5	8.26X10-6	1.57X10-1	2.42X10-1		
rs11730757	4	138910812	4.05X10-5	1.39X10-1	6.54X10-1	3.48X10-6		
rs3766509	1	145596899	4.07X10-5	8.66X10-4	3.54X10-2	1.04X10-2	ACP6	ENSG00000162836
rs3737843	1	145554345	4.08X10-5	2.09X10-3	2.46X10-2	6.20X10-3	BCL9	ENSG00000116128
rs1505129	18	73982506	4.24X10-5	9.08X10-6	1.44X10-1	2.54X10-1		
rs12454691	18	73979874	4.29X10-5	1.00X10-5	1.38X10-1	2.45X10-1		
rs12457511	18	73981374	4.29X10-5	9.96X10-6	1.38X10-1	2.46X10-1		

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rs12526319	6	103172663	4.52X10-5	3.04X10-2	1.42X10-3	8.30X10-3		
rs6699536	1	101049132	4.52X10-5	2.57X10-3	2.86X10-3	4.88X10-2		
rs7450158	6	103176780	4.54X10-5	3.20X10-2	1.32X10-3	8.51X10-3		
rs12719344	5	125404676	4.55X10-5	1.37X10-4	6.28X10-1	4.21X10-3		
rs9285553	6	103175472	4.59X10-5	3.21X10-2	1.32X10-3	8.60X10-3		
rs11263678	15	20558548	4.72X10-5	4.08X10-4	4.56X10-1	2.03X10-3	NIPA2	ENSG00000140157
rs6571042	6	103217861	4.75X10-5	4.86X10-2	5.73X10-4	1.36X10-2		
rs1890579	6	159779507	4.87X10-5	1.56X10-1	1.14X10-4	2.20X10-2		
rs17039614	2	2345564	4.96X10-5	8.83X10-4	8.45X10-1	5.35X10-4		
rs4629584	5	152162278	4.97X10-5	2.23X10-5	4.51X10-1	3.98X10-2	LINC01470	ENSG00000249484
rs11743031	5	152195623	4.97X10-5	2.84X10-5	6.55X10-1	2.15X10-2	LINC01470	ENSG00000249484
rs4512127	5	152192652	4.99X10-5	2.84X10-5	6.55X10-1	2.16X10-2	LINC01470	ENSG00000249484
rs2978521	8	62279233	5.04X10-5	4.38X10-3	6.80X10-3	1.36X10-2	CLVS1	ENSG00000177182
rs6571045	6	103234957	5.11X10-5	8.63X10-2	7.24X10-4	6.60X10-3		
rs7455007	6	103238946	5.13X10-5	8.58X10-2	7.24X10-4	6.67X10-3		
rs9377379	6	103233198	5.14X10-5	8.67X10-2	7.24X10-4	6.62X10-3		
rs7450897	6	103230477	5.15X10-5	8.70X10-2	7.24X10-4	6.61X10-3		
rs6571044	6	103234938	5.15X10-5	8.64X10-2	7.24X10-4	6.66X10-3		
rs4460127	5	152163941	5.20X10-5	2.18X10-5	8.35X10-1	2.31X10-2	LINC01470	ENSG00000249484
rs11617728	13	24882356	5.23X10-5	4.77X10-5	1.18X10-2	7.54X10-1	ATP8A2	ENSG00000132932
rs1396672	4	138923473	5.33X10-5	1.38X10-1	8.09X10-1	3.88X10-6		
rs7449573	6	103189846	5.40X10-5	7.78X10-2	7.82X10-4	7.23X10-3		

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rs2931331	8	62286060	5.45X10-5	2.53X10-3	6.39X10-3	2.75X10-2	CLVS1	ENSG00000177182
rs3942245	2	2350331	5.51X10-5	4.33X10-4	6.17X10-1	1.69X10-3		
rs2978535	8	62281668	5.63X10-5	2.54X10-3	6.75X10-3	2.69X10-2		ENSG00000177182
rs7651862	3	65069950	5.64X10-5	2.36X10-2	1.10X10-1	1.78X10-4		
rs4524565	5	152241237	5.65X10-5	1.18X10-5	6.88X10-1	5.69X10-2	LINC01470	ENSG00000249484
rs7451370	6	103186935	5.71X10-5	5.95X10-2	7.95X10-4	9.90X10-3		
rs9404226	6	103204373	5.83X10-5	8.80X10-2	7.60X10-4	7.19X10-3		
rs7746320	6	103194912	5.96X10-5	8.81X10-2	7.76X10-4	7.20X10-3		
rs1051992	11	6297282	6.07X10-5	3.90X10-4	4.21X10-2	3.07X10-2	PRKCDBP	ENSG00000170955
rs2241006	12	9639476	6.11X10-5	8.48X10-2	3.41X10-4	1.75X10-2	KLRB1	ENSG00000111796
rs1537720	9	116937364	6.13X10-5	6.72X10-5	9.27X10-2	8.16X10-2	RP11-532L1.2	ENSG00000236461
rs2676622	9	114494325	6.26X10-5	4.58X10-5	1.33X10-2	8.56X10-1	INIP	ENSG00000148153
rs9511787	13	24881592	6.30X10-5	1.67X10-4	9.10X10-3	3.45X10-1	ATP8A2	ENSG00000132932
rs6903735	6	103254295	6.32X10-5	6.87X10-2	1.40X10-3	5.48X10-3		
rs12052006	18	51696461	6.46X10-5	5.71X10-6	1.73X10-1	5.46X10-1	LIC01416	ENSG00000260930
rs1571046	1	101071804	6.52X10-5	2.65X10-3	4.41X10-3	4.67X10-2		
rs9511790	13	24887752	6.53X10-5	1.21X10-4	4.84X10-3	9.36X10-1	ATP8A2	ENSG00000132932
rs9319747	18	51700096	6.65X10-5	5.87X10-6	1.92X10-1	4.95X10-1	LIC01416	ENSG00000260930
rs11962340	6	103299445	6.76X10-5	6.42X10-2	1.95X10-3	4.56X10-3		
rs2978505	8	62261719	6.90X10-5	7.67X10-3	3.59X10-3	2.11X10-2	CLVS1	ENSG00000177182
rs10844140	12	9638555	6.95X10-5	8.60X10-2	2.68X10-4	2.55X10-2	KLRB1	ENSG00000111796
rs6577209	1	101027668	7.09X10-5	1.89X10-3	4.50X10-3	7.09X10-2		

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rs11740092	5	152165624	7.31X10-5	3.35X10-5	8.37X10-1	2.22X10-2	LINC01470	ENSG00000249484
rs12867463	13	24881768	7.48X10-5	1.67X10-4	8.68X10-3	4.42X10-1	ATP8A2	ENSG00000132932
rs11846469	14	39750884	7.49X10-5	7.25X10-2	2.15X10-3	4.11X10-3		
rs12889928	14	39751650	7.51X10-5	7.25X10-2	2.16X10-3	4.10X10-3		
rs4129242	6	103192235	7.62X10-5	8.83X10-2	1.04X10-3	7.13X10-3		
rs4907399	8	142624890	7.78X10-5	2.71X10-2	4.65X10-2	5.30X10-4		
rs10810259	9	14821864	7.80X10-5	2.80X10-4	1.62X10-1	1.48X10-2	FREM1	ENSG00000164946
rs17214448	4	76702005	7.92X10-5	1.99X10-5	3.99X10-1	8.58X10-2	C4orf26	ENSG00000174792
rs9511786	13	24881275	7.98X10-5	1.68X10-4	9.29X10-3	4.42X10-1	ATP8A2	ENSG00000132932
rs9456749	6	162518420	8.04X10-5	1.37X10-3	1.23X10-1	4.11X10-3	PARK2	ENSG00000185345
rs11734102	4	76701191	8.08X10-5	1.98X10-5	4.02X10-1	8.79X10-2	C4orf26	ENSG00000174792
rs6811713	4	76701395	8.13X10-5	1.99X10-5	4.06X10-1	8.72X10-2	C4orf26	ENSG00000174792
rs1414137	9	116945474	8.27X10-5	7.10X10-5	1.42X10-1	7.13X10-2	RP11-532L1.2	ENSG00000236461
rs13167390	5	152162761	8.37X10-5	2.21X10-5	8.26X10-1	3.98X10-2	LINC01470	ENSG00000249484
rs1135816	12	9641936	8.46X10-5	1.07X10-1	3.77X10-4	1.83X10-2	KLRB1	ENSG00000111796
rs10518644	1	80652485	8.55X10-5	1.73X10-2	1.19X10-2	3.61X10-3		
rs1994519	11	6298324	8.60X10-5	5.30X10-4	4.56X10-2	3.11X10-2	PRKCDBP	ENSG00000170955
rs4736874	8	40576152	8.61X10-5	1.66X10-2	3.14X10-1	1.44X10-4	ZMAT4	ENSG00000165061
rs7216020	17	30121041	8.62X10-5	2.66X10-2	3.22X10-2	8.80X10-4		
rs1523415	6	103264532	8.66X10-5	7.73X10-2	1.98X10-3	4.93X10-3		
rs1523408	6	103268815	8.72X10-5	7.73X10-2	1.98X10-3	4.97X10-3		
rs10743737	12	9514883	8.82X10-5	1.09X10-1	1.25X10-4	5.67X10-2	RP11-726G1.1	ENSG00000214776

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rs2051090	13	35352193	8.83X10-5	4.25X10-2	2.99X10-1	6.09X10-5	DCLK1	ENSG00000133083
rs7248327	19	13497913	8.90X10-5	3.84X10-2	1.98X10-3	1.03X10-2	CACNA1A	ENSG00000141837
rs8028189	15	20575442	8.92X10-5	5.76X10-4	5.53X10-1	2.46X10-3	NIPA2	ENSG00000140157
rs10102149	8	104883444	8.92X10-5	1.08X10-1	3.81X10-3	1.91X10-3	RIMS2	ENSG00000176406
rs3809572	15	65143828	8.97X10-5	3.91X10-5	1.83X10-1	1.10X10-1	RP11-798K3.2	ENSG00000259347
rs10834971	11	26337381	9.04X10-5	9.63X10-4	9.92X10-2	8.32X10-3	ANO3	ENSG00000134343
rs1008560	22	20887954	9.22X10-5	1.33X10-1	1.51X10-2	4.04X10-4	IGLVI-56	ENSG00000253126
rs7170784	15	20572554	9.27X10-5	5.18X10-4	5.80X10-1	2.72X10-3	NIPA2	ENSG00000140157
rs1823803	2	234203850	9.31X10-5	3.74X10-4	3.40X10-2	6.48X10-2	UGT1A8	ENSG00000242366
rs12300846	12	9634751	9.48X10-5	4.32X10-2	5.83X10-4	3.34X10-2	KLRB1	ENSG00000111796
rs11638002	15	65129033	9.53X10-5	3.90X10-5	1.85X10-1	1.17X10-1	RP11-798K3.2	ENSG00000259347
rs1936002	13	35354084	9.68X10-5	4.28X10-2	2.99X10-1	6.73X10-5	DCLK1	ENSG00000133083
rs3000528	10	133922016	9.71X10-5	1.18X10-5	2.33X10-1	3.14X10-1	STK32C	ENSG00000165752
rs2685501	17	53256676	9.71X10-5	1.28X10-3	7.74X10-1	8.72X10-4	RP11-60A24.3	ENSG00000265542
rs9545602	13	35354503	9.72X10-5	4.29X10-2	2.99X10-1	6.75X10-5	DCLK1	ENSG00000133083
rs4734731	8	104904087	9.79X10-5	0.108	3.80X10-3	2.12X10-3	RIMS2	ENSG00000176406
rs9545604	13	35354942	9.79X10-5	4.32X10-2	2.99X10-1	6.75X10-5	DCLK1	ENSG00000133083
rs4943350	13	35351860	9.91X10-5	4.39X10-2	0.299	6.74X10-5	DCLK1	ENSG00000133083

Table E6. Two df test results in the discovery cohorts for the four SNPs close to the *MAGII* gene and the eight SNPs with $p < 0.05$ in CHS.

SNP	CHR	POS	Meta-analysis p-value	p-value BAMSE	p-value PIAMA	p-value GINI/LISA	Gene
rs7651862	3	65069950	5.64×10^{-5}	0.02	0.11	1.78×10^{-4}	<i>MAGII</i>
rs11706125	3	65069843	1.11×10^{-4}	0.02	0.11	3.89×10^{-4}	<i>MAGII</i>
rs11718057	3	65069823	1.21×10^{-4}	0.02	0.11	4.29×10^{-4}	<i>MAGII</i>
rs13066946	3	65070988	1.24×10^{-4}	0.02	0.11	4.32×10^{-4}	<i>MAGII</i>
rs686237	20	47804141	0.005	0.006	0.261	0.049	<i>B4GALT5</i> ,
rs1057251	18	32102579	0.004	0.034	0.062	0.033	<i>MOCOS</i>
rs12455842	18	32096284	0.004	0.032	0.074	0.032	<i>MOCOS</i>
rs4143882	5	7717364	0.006	0.056	0.083	0.027	<i>ADCY2</i>
rs727432	5	7716078	0.008	0.073	0.088	0.027	<i>ADCY2</i>
rs6886921	5	7718539	0.001	0.027	0.079	0.009	<i>ADCY2</i>
rs12457919	18	32108100	0.004	0.033	0.061	0.034	<i>MOCOS</i>
rs963146	11	83423444	0.002	0.039	0.035	0.021	<i>DLG2</i>

Table E7. Statistically significant SNPs in CAPPS/SAGE from the genome-wide interaction analysis of the association between SNP \times NO₂ interaction and asthma.

								Discovery GWIS meta-analysis	Look-up	
								n=1,534	CHS n=1,602	CAPPS/SAGE n=186
Chr	SNP	Position (build 37)	Minor Allele	Major Allele	MAF	Nearest gene	Feature	p-value*	p-value [†]	p-value [†]
4	rs3843891	138828912	C	A	0.47	<i>PCDH18</i> , <i>SLC7A11</i>	-	2.49x10 ⁻⁵	0.67	0.037
8	rs17265947	63901079	G	A	0.17	<i>NKAIN3</i>	Intron	4.65x10 ⁻⁵	0.30	0.044

Shown are SNPs with $p < 0.05$ in CAPPS/SAGE, ordered by p-value. All p-values given are two-sided. Chr, chromosome; Minor Allele, according to discovery phase cohorts; MAF, minor allele frequency according to BAMSE. * Genome-wide significance threshold, $p < 7.2 \times 10^{-8}$. [†]Significance threshold, $p < 0.05$.

Table E8. Main effects of SNPs that were statistically significant ($p < 0.05$) in the look-up evaluation in CHS, showing beta coefficients and standard errors.

		Discovery GWIS meta-analysis			Look-up					
		BAMSE, GINI/LISA, PIAMA, n=1,534			CHS n=1,602			CAPPS/SAGE n=186		
Chr	SNP	Combined coef (direction)*	Combined se*	Combined p-value†	coef	se	p-value	coef	se	p-value
20	rs686237	-0.096 (---)	0.104	0.272	-0.016	0.081	0.847	NA	NA	NA
18	rs1057251	-0.104 (---)	0.160	0.414	-0.062	0.117	0.598	0.022	0.333	0.948
18	rs12455842	-0.133 (---)	0.161	0.344	-0.069	0.118	0.560	0.059	0.329	0.857
5	rs4143882	-0.015 (---)	0.103	0.619	0.030	0.078	0.697	0.017	0.196	0.932
5	rs727432	0.009 (++)	0.103	0.651	-0.027	0.077	0.728	-0.016	0.196	0.937
5	rs6886921	0.013 (++)	0.102	0.612	-0.044	0.078	0.576	NA	NA	NA
18	rs12457919	0.107 (++)	0.163	0.419	0.069	0.123	0.573	NA	NA	NA
11	rs963146	0.146 (++)	0.113	0.284	-0.050	0.091	0.581	0.097	0.229	0.673

Chr, chromosome; NA, not available. *Metal meta-analysis based on standard errors and estimated effect size for each marker. This analysis assumes consistent effect sizes across studies and was done in order to obtain combined coefficient and combined standard errors for the discovery cohorts. †Metal meta-analysis based on direction of effect for tested allele and corresponding p-value using sample size weighted analysis.

384 **Table E9.** Interaction effects of SNPs that were statistically significant ($p < 0.05$) in the look-up evaluation in CHS, showing beta
 385 coefficients and standard errors.

		Discovery GWIS meta-analysis			Look-up					
		BAMSE, GINI/LISA, PIAMA, n=1,534			CHS, n=1,602			CAPPS/SAGE, n=186		
Chr	SNP	Combined coef (direction)*	Combined se*	Combined p-value†	coef	se	p-value	coef	se	p-value
20	rs686237	0.683 (+++)	0.170	5.43×10^{-5}	-0.253	0.080	0.0016	NA	NA	NA
18	rs1057251	-1.210 (---)	0.324	6.18×10^{-5}	0.310	0.119	0.0094	-0.545	0.987	0.581
18	rs12455842	-1.215 (---)	0.327	6.10×10^{-5}	0.306	0.119	0.01	-0.587	0.983	0.550
5	rs4143882	0.699 (+++)	0.174	4.75×10^{-5}	0.185	0.076	0.015	-0.569	0.510	0.264
5	rs727432	-0.682 (---)	0.174	6.67×10^{-5}	-0.183	0.076	0.016	0.564	0.509	0.268
5	rs6886921	-0.769 (---)	0.177	7.03×10^{-6}	-0.183	0.076	0.016	NA	NA	NA
18	rs12457919	1.246 (+++)	0.329	5.52×10^{-5}	-0.312	0.124	0.012	NA	NA	NA
11	rs963146	0.757 (+++)	0.209	8.61×10^{-5}	-0.186	0.088	0.034	-0.227	0.457	0.619

386 Chr, chromosome; NA, not available. *Metal meta-analysis based on standard errors and estimated effect size for each marker. This
 387 analysis assumes consistent effect sizes across studies and was done in order to obtain combined coefficient and combined standard
 388 errors for the discovery cohorts. †Metal meta-analysis based on direction of effect for tested allele and corresponding p-value using
 389 sample size weighted analysis.

Table E10. cis-eQTL analysis of association between the 8 top SNPs and expression of genes located within 500k base-pairs of the particular SNP in lung-tissue from 1,111 adults who underwent lung surgery at three academic sites.

Chr	HUGO Gene Symbol	SNP	SNP Position	Ref. A1	Ref. A2	Affymetrix ID CIS-genes	Chr Start, Affy array	Chr end, Affy array	beta GRO	se GRO	P GRO	Beta LAV	Se LAV	P LAV	Beta UBC	Se UBC	P UBC	Beta meta-analysis	Se meta-analysis	P meta-analysis
5	<i>C5orf49</i>	rs727432	7716078	T	G	100307940_TG I_at	7884637	7904173	0.15	0.11	0.16	0.10	0.14	0.47	0.33	0.13	0.01	0.19	0.07	0.01
5	<i>C5orf49</i>	rs727432	7716078	T	G	100154445_TG I_at	7884510	7904264	0.11	0.13	0.41	0.16	0.15	0.29	0.40	0.14	0.01	0.21	0.08	0.01
5	<i>C5orf49</i>	rs727432	7716078	T	G	100300265_TG I_at	7883750	7904603	0.16	0.10	0.10	0.11	0.12	0.33	0.17	0.12	0.15	0.15	0.06	0.02
5	<i>ADCY2</i>	rs727432	7716078	T	G	100138993_TG I_at	7449383	7880644	0.15	0.09	0.09	0.10	0.10	0.33	0.07	0.11	0.54	0.11	0.06	0.05
5	<i>MTRR</i>	rs727432	7716078	T	G	100308573_TG I_at	7950283	7953642	-0.07	0.10	0.49	-0.05	0.13	0.69	-0.16	0.10	0.11	-0.10	0.06	0.11
5	<i>FASTK D3</i>	rs727432	7716078	T	G	100157808_TG I_at	7912272	7922115	0.12	0.13	0.38	0.28	0.16	0.08	-0.04	0.22	0.86	0.15	0.09	0.11
5	<i>MTRR</i>	rs727432	7716078	T	G	100141139_TG I_at	7922216	7954233	-0.11	0.14	0.43	0.33	0.15	0.03	0.01	0.18	0.96	0.07	0.09	0.43
5		rs727432	7716078	T	G	100123278_TG I_at	7556919	7557406	-0.04	0.12	0.75	0.04	0.12	0.76	-0.20	0.16	0.22	-0.04	0.08	0.56
5	<i>ADCY2</i>	rs727432	7716078	T	G	100128975_TG I_at	7449342	7883194	-0.03	0.13	0.80	0.02	0.10	0.87	-0.04	0.17	0.82	-0.01	0.07	0.90
5	<i>C5orf49</i>	rs4143882	7717364	A	G	100154445_TG I_at	7884510	7904264	0.06	0.10	0.58	0.11	0.10	0.30	0.25	0.11	0.02	0.13	0.06	0.03
5	<i>C5orf49</i>	rs4143882	7717364	A	G	100307940_TG I_at	7884637	7904173	0.08	0.08	0.32	0.06	0.10	0.52	0.20	0.10	0.04	0.11	0.05	0.03
5	<i>MTRR</i>	rs4143882	7717364	A	G	100308573_TG I_at	7950283	7953642	-0.08	0.08	0.32	-0.10	0.09	0.24	-0.08	0.08	0.27	-0.09	0.05	0.06
5	<i>FASTK D3</i>	rs4143882	7717364	A	G	100157808_TG I_at	7912272	7922115	0.07	0.11	0.51	0.18	0.11	0.09	0.10	0.17	0.57	0.12	0.07	0.08
5	<i>C5orf49</i>	rs4143882	7717364	A	G	100300265_TG I_at	7883750	7904603	0.10	0.08	0.22	0.08	0.08	0.30	0.06	0.09	0.50	0.08	0.05	0.09
5	<i>ADCY2</i>	rs4143882	7717364	A	G	100138993_TG I_at	7449383	7880644	0.12	0.07	0.08	0.03	0.07	0.64	0.02	0.08	0.82	0.06	0.04	0.14
5		rs4143882	7717364	A	G	100123278_TG I_at	7556919	7557406	0.04	0.10	0.69	0.07	0.08	0.37	-0.09	0.12	0.47	0.03	0.06	0.61
5	<i>MTRR</i>	rs4143882	7717364	A	G	100141139_TG I_at	7922216	7954233	-0.22	0.11	0.05	0.23	0.10	0.03	-0.07	0.13	0.58	-0.01	0.07	0.93
5	<i>ADCY2</i>	rs4143882	7717364	A	G	100128975_TG I_at	7449342	7883194	-0.03	0.10	0.78	0.00172	0.07	0.98	0.07	0.13	0.57	0.00351	0.05	0.95
5	<i>C5orf49</i>	rs6886921	7718539	T	C	100307940_TG I_at	7884637	7904173	0.12	0.10	0.26	0.08	0.13	0.55	0.31	0.12	0.01	0.17	0.07	0.01
5	<i>C5orf49</i>	rs6886921	7718539	T	C	100300265_TG I_at	7883750	7904603	0.14	0.10	0.15	0.15	0.11	0.16	0.15	0.11	0.18	0.15	0.06	0.02
5	<i>C5orf49</i>	rs6886921	7718539	T	C	100154445_TG I_at	7884510	7904264	0.08	0.13	0.54	0.10	0.14	0.45	0.38	0.14	0.01	0.18	0.08	0.02
5	<i>ADCY2</i>	rs6886921	7718539	T	C	100138993_TG I_at	7449383	7880644	0.16	0.09	0.06	0.10	0.10	0.32	0.08	0.11	0.48	0.12	0.06	0.03
5	<i>FASTK D3</i>	rs6886921	7718539	T	C	100157808_TG I_at	7912272	7922115	0.14	0.13	0.30	0.27	0.15	0.06	-0.03	0.22	0.91	0.16	0.09	0.07

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5	MTRR	rs688692 1	771853 9	T	C	100308573_TG I_at	795028 3	795364 2	-0.06	0.0 9	0.56	0.0033 5	0.1 2	0.98	-0.16	0.1 0	0.10	-0.08	0.06	0.17
5		rs688692 1	771853 9	T	C	100123278_TG I_at	755691 9	755740 6	-0.02	0.1 2	0.88	0.01	0.1 1	0.92	-0.20	0.1 6	0.20	-0.04	0.07	0.54
5	ADCY2	rs688692 1	771853 9	T	C	100128975_TG I_at	744934 2	788319 4	-0.07	0.1 3	0.60	-0.01	0.0 9	0.93	-0.04	0.1 7	0.83	-0.03	0.07	0.66
5	MTRR	rs688692 1	771853 9	T	C	100141139_TG I_at	792221 6	795423 3	-0.13	0.1 3	0.32	0.23	0.1 4	0.10	0.001 18	0.1 8	0.99	0.03	0.09	0.72
11	DLG2	rs963146	834234 44	A	G	100304239_TG I_at	828485 09	837058 36	0.08	0.1 0	0.42	0.04	0.0 9	0.66	0.04	0.1 1	0.72	0.05	0.06	0.35
11	DLG2	rs963146	834234 44	A	G	100155681_TG I_at	828437 00	843121 13	0.05	0.0 7	0.55	-0.20	0.0 9	0.02	0.01	0.0 8	0.90	-0.03	0.05	0.46
18	SLC39A 6	rs124558 42	320962 84	T	C	100303106_TG I_at	319449 60	319633 55	0.21	0.0 7	0.00271	0.11	0.1 1	0.33	0.05	0.1 2	0.67	0.16	0.05	0.0030 [†]
18	RPRD1 A	rs124558 42	320962 84	T	C	100145446_TG I_at	318595 59	319015 17	0.07	0.0 6	0.26	0.18	0.1 0	0.08	0.03	0.0 8	0.66	0.08	0.04	0.07
18	FHOD3	rs124558 42	320962 84	T	C	100132210_TG I_at	321316 99	326140 16	0.02	0.0 4	0.62	0.20	0.0 8	0.02	0.04	0.0 6	0.57	0.05	0.03	0.12
18	MOCO S	rs124558 42	320962 84	T	C	100138664_TG I_at	320214 77	321026 83	0.0041	0.0 2	0.86	-0.04	0.0 3	0.19	-0.05	0.0 3	0.13	-0.02	0.02	0.18
18	SLC39A 6	rs124558 42	320962 84	T	C	100149921_TG I_at	319431 96	319632 03	-0.01	0.0 8	0.90	0.23	0.1 6	0.15	0.20	0.1 3	0.14	0.08	0.06	0.24
18	RPRD1 A	rs124558 42	320962 84	T	C	100158423_TG I_at	318237 89	319013 71	0.06	0.1 1	0.59	0.08	0.1 9	0.68	0.003 72	0.1 6	0.98	0.05	0.08	0.55
18	ELP2	rs124558 42	320962 84	T	C	100140463_TG I_at	319638 84	320086 05	-0.08	0.1 0	0.44	0.24	0.1 9	0.23	0.21	0.1 5	0.18	0.04	0.08	0.57
18	RPRD1 A	rs124558 42	320962 84	T	C	100302024_TG I_at	318237 89	319013 71	-0.02	0.1 1	0.85	-0.33	0.2 2	0.13	0.08	0.1 8	0.67	-0.05	0.09	0.59
18		rs124558 42	320962 84	T	C	100146554_TG I_at	321039 34	321061 09	0.01	0.0 4	0.75	0.05	0.0 6	0.44	-0.05	0.0 6	0.41	0.01	0.03	0.83
18	SLC39A 6	rs124558 42	320962 84	T	C	100129017_TG I_at	319431 28	319480 90	0.0023 0	0.0 8	0.98	0.15	0.1 7	0.38	-0.08	0.1 3	0.56	0.0042 7	0.06	0.95
18	RPRD1 A	rs124558 42	320962 84	T	C	100136421_TG I_at	318258 08	319015 20	0.04	0.0 6	0.57	0.01	0.1 1	0.94	-0.15	0.1 2	0.20	0.0031 2	0.05	0.95
18		rs124558 42	320962 84	T	C	100138044_TG I_at	320092 21	320118 88	-0.06	0.0 8	0.46	0.01	0.1 6	0.95	0.15	0.1 4	0.27	0.0020 1	0.06	0.98
18	FHOD3	rs105725 1	321025 79	T	C	100132210_TG I_at	321316 99	326140 16	0.06	0.0 6	0.32	0.21	0.0 9	0.02	0.04	0.0 8	0.66	0.09	0.04	0.03
18	MOCO S	rs105725 1	321025 79	T	C	100138664_TG I_at	320214 77	321026 83	-0.03	0.0 3	0.36	-0.03	0.0 3	0.28	-0.06	0.0 4	0.13	-0.04	0.02	0.05
18	SLC39A 6	rs105725 1	321025 79	T	C	100303106_TG I_at	319449 60	319633 55	0.15	0.1 0	0.13	0.10	0.1 2	0.38	0.09	0.1 5	0.54	0.12	0.07	0.07
18	SLC39A 6	rs105725 1	321025 79	T	C	100149921_TG I_at	319431 96	319632 03	0.03	0.1 2	0.82	0.27	0.1 6	0.10	0.25	0.1 7	0.16	0.14	0.08	0.09
18	SLC39A 6	rs105725 1	321025 79	T	C	100129017_TG I_at	319431 28	319480 90	0.23	0.1 2	0.05	0.15	0.1 7	0.38	-0.11	0.1 7	0.53	0.13	0.08	0.13
18	RPRD1 A	rs105725 1	321025 79	T	C	100145446_TG I_at	318595 59	319015 17	0.04	0.0 9	0.64	0.18	0.1 1	0.08	0.02	0.1 0	0.81	0.08	0.06	0.17
18	RPRD1 A	rs105725 1	321025 79	T	C	100158423_TG I_at	318237 89	319013 71	0.19	0.1 5	0.21	0.11	0.1 9	0.56	-0.03	0.2 1	0.88	0.11	0.10	0.28
18	RPRD1 A	rs105725 1	321025 79	T	C	100136421_TG I_at	318258 08	319015 20	0.15	0.0 9	0.10	-0.01	0.1 1	0.95	-0.17	0.1 5	0.27	0.04	0.06	0.51

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18		rs105725 1	321025 79	T	C	100138044_TG I_at	320092 21	320118 88	0.0026 1	0.1 2	0.98	-0.03	0.1 6	0.86	0.19	0.1 8	0.28	0.04	0.08	0.68
18		rs105725 1	321025 79	T	C	100146554_TG I_at	321039 34	321061 09	0.02	0.0 6	0.76	0.05	0.0 6	0.42	-0.06	0.0 8	0.46	0.01	0.04	0.73
18	RPRD1 A	rs105725 1	321025 79	T	C	100302024_TG I_at	318237 89	319013 71	0.12	0.1 6	0.45	-0.33	0.2 2	0.13	0.07	0.2 4	0.77	-0.01	0.11	0.93
18	ELP2	rs105725 1	321025 79	T	C	100140463_TG I_at	319638 84	320086 05	-0.26	0.1 5	0.08	0.25	0.2 0	0.21	0.21	0.2 0	0.30	0.0036 3	0.10	0.97
18	FHOD3	rs124579 19	321081 00	A	C	100132210_TG I_at	321316 99	326140 16	0.06	0.0 6	0.32	0.21	0.0 9	0.02	0.04	0.0 8	0.66	0.09	0.04	0.03
18	MOCO S	rs124579 19	321081 00	A	C	100138664_TG I_at	320214 77	321026 83	-0.03	0.0 3	0.36	-0.03	0.0 3	0.28	-0.06	0.0 4	0.13	-0.04	0.02	0.05
18	SLC39A 6	rs124579 19	321081 00	A	C	100303106_TG I_at	319449 60	319633 55	0.15	0.1 0	0.13	0.10	0.1 2	0.38	0.09	0.1 5	0.54	0.12	0.07	0.07
18	SLC39A 6	rs124579 19	321081 00	A	C	100149921_TG I_at	319431 96	319632 03	0.03	0.1 2	0.82	0.27	0.1 6	0.10	0.25	0.1 7	0.16	0.14	0.08	0.09
18	SLC39A 6	rs124579 19	321081 00	A	C	100129017_TG I_at	319431 28	319480 90	0.23	0.1 2	0.05	0.15	0.1 7	0.38	-0.11	0.1 7	0.53	0.13	0.08	0.13
18	RPRD1 A	rs124579 19	321081 00	A	C	100145446_TG I_at	318595 59	319015 17	0.04	0.0 9	0.64	0.18	0.1 1	0.08	0.02	0.1 0	0.81	0.08	0.06	0.17
18	RPRD1 A	rs124579 19	321081 00	A	C	100158423_TG I_at	318237 89	319013 71	0.19	0.1 5	0.21	0.11	0.1 9	0.56	-0.03	0.2 1	0.88	0.11	0.10	0.28
18	RPRD1 A	rs124579 19	321081 00	A	C	100136421_TG I_at	318258 08	319015 20	0.15	0.0 9	0.10	-0.01	0.1 1	0.95	-0.17	0.1 5	0.27	0.04	0.06	0.51
18		rs124579 19	321081 00	A	C	100138044_TG I_at	320092 21	320118 88	0.0026 1	0.1 2	0.98	-0.03	0.1 6	0.86	0.19	0.1 8	0.28	0.04	0.08	0.68
18		rs124579 19	321081 00	A	C	100146554_TG I_at	321039 34	321061 09	0.02	0.0 6	0.76	0.05	0.0 6	0.42	-0.06	0.0 8	0.46	0.01	0.04	0.73
18	RPRD1 A	rs124579 19	321081 00	A	C	100302024_TG I_at	318237 89	319013 71	0.12	0.1 6	0.45	-0.33	0.2 2	0.13	0.07	0.2 4	0.77	-0.01	0.11	0.93
18	ELP2	rs124579 19	321081 00	A	C	100140463_TG I_at	319638 84	320086 05	-0.26	0.1 5	0.08	0.25	0.2 0	0.21	0.21	0.2 0	0.30	0.0036 3	0.10	0.97
20	B4GAL T5	rs686237	478041 41	C	A	100313047_TG I_at	476833 94	476854 34	0.28	0.0 8	2.88x10 -4	0.49	0.0 9	3.45x1 08	0.51	0.0 9	1.99x1 08	0.41	0.05	1.18x10- 17 ⁺
20	SLC9A8	rs686237	478041 41	C	A	100308978_TG I_at	479385 47	479388 76	0.05	0.1 5	0.74	-0.23	0.1 4	0.10	-0.36	0.1 7	0.03	-0.17	0.09	0.05
20	B4GAL T5	rs686237	478041 41	C	A	100302697_TG I_at	476828 89	477638 28	0.12	0.1 6	0.45	0.29	0.2 0	0.14	0.17	0.1 9	0.36	0.18	0.10	0.07
20		rs686237	478041 41	C	A	100162632_TG I_at	477475 39	477478 81	0.08	0.0 9	0.36	-0.19	0.1 0	0.07	-0.18	0.1 1	0.08	-0.07	0.06	0.19
20	SPATA 2	rs686237	478041 41	C	A	100137358_TG I_at	479547 72	479654 52	0.07	0.1 3	0.59	0.05	0.2 2	0.81	0.35	0.2 3	0.12	0.12	0.10	0.22
20	SPATA 2	rs686237	478041 41	C	A	100133421_TG I_at	479533 37	479654 75	0.0023 0	0.1 3	0.99	0.32	0.1 8	0.08	-0.04	0.1 9	0.85	0.07	0.09	0.43
20	SLC9A8	rs686237	478041 41	C	A	100140649_TG I_at	478626 56	479421 79	0.21	0.1 5	0.17	-0.28	0.1 9	0.14	0.15	0.1 8	0.40	0.06	0.10	0.56
20	RNF11 4	rs686237	478041 41	C	A	100155758_TG I_at	479863 20	480038 27	-0.02	0.1 9	0.91	0.29	0.3 3	0.38	0.06	0.2 6	0.81	0.06	0.14	0.68
20	PTGIS	rs686237	478041 41	C	A	100143106_TG I_at	475538 17	476181 14	-0.13	0.0 9	0.16	0.10	0.1 2	0.37	0.02	0.1 1	0.88	-0.02	0.06	0.69

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20	<i>SLC9A8</i>	rs686237	478041 41	C	A	100152866_TG I_at	479279 40	479403 38	0.18	0.1 7	0.27	-0.08	0.2 2	0.73	-0.11	0.2 4	0.65	0.04	0.12	0.71
20	<i>SLC9A8</i>	rs686237	478041 41	C	A	100308967_TG I_at	479408 39	479413 54	0.0018 6	0.1 6	0.99	0.16	0.1 7	0.36	-0.09	0.2 1	0.67	0.03	0.10	0.74
20	<i>SH</i>	rs686237	478041 41	C	A	100127534_TG I_at	480329 33	480388 25	0.05	0.0 7	0.48	0.0025 0	0.0 9	0.98	-0.02	0.0 8	0.82	0.01	0.04	0.74
20		rs686237	478041 41	C	A	100146092_TG I_at	476214 59	476218 78	-0.02	0.0 6	0.73	0.05	0.0 8	0.57	-0.05	0.0 9	0.55	-0.01	0.04	0.82
20	<i>RNF11</i> 4	rs686237	478041 41	C	A	100162528_TG I_at	479863 56	480020 83	-0.06	0.1 5	0.67	0.16	0.2 3	0.49	-0.08	0.1 9	0.70	-0.02	0.11	0.84

Adjusted for age, gender, smoking, and disease (e.g. COPD), principal components explaining > 1% of variance (to remove possible noise/variation due to technical factors). GRO, University of Groningen; LAV, Laval University; UBC, University of British Columbia. * Cis-eQTL analysis of genes located within 500,000 bp of the SNPs (using imputed data). †Significant after correction for multiple testing using the Bonferroni method (0.05/12=0.0042) ‡significant after correction for multiple testing using the Bonferroni method (0.05/14=0.0036)..

397 **Table E11.** Cis-eQTL analysis of association between the 8 top SNPs and expression of genes located within 500k base-pairs of the
 398 particular SNP in whole blood from the GTEx database.

Chr	Gene Symbol	Gencode Id	SNP	p-value	Effect Size	T-Statistic	Standard Error
20	B4GALT5	ENSG00000158470.5	rs686237	0.0004*	-0.1	-3.6	0.029
5	ADCY2	ENSG00000078295.11	rs6886921	0.00045*	-0.19	-3.5	0.053
5	ADCY2	ENSG00000078295.11	rs727432	0.00048*	-0.19	-3.5	0.054
5	ADCY2	ENSG00000078295.11	rs4143882	0.0012*	-0.18	-3.3	0.055
18	ELP2	ENSG00000134759.9	rs1057251	0.15	-0.098	-1.4	0.068
18	ELP2	ENSG00000134759.9	rs12455842	0.15	-0.098	-1.4	0.068
18	ELP2	ENSG00000134759.9	rs12457919	0.15	-0.098	-1.4	0.068
20	PTGIS	ENSG00000124212.5	rs686237	0.15	0.075	1.5	0.052
20	SLC9A8	ENSG00000197818.7	rs686237	0.17	-0.04	-1.4	0.029
5	FASTKD3	ENSG00000124279.7	rs6886921	0.22	0.038	1.2	0.031
5	FASTKD3	ENSG00000124279.7	rs727432	0.23	0.038	1.2	0.031
5	MTRR	ENSG00000124275.10	rs727432	0.31	0.036	1	0.035

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5	MTRR	ENSG00000124275.10	rs727432	0.31	0.036	1	0.035
5	MTRR	ENSG00000124275.10	rs6886921	0.41	0.029	0.83	0.035
5	MTRR	ENSG00000124275.10	rs4143882	0.42	0.029	0.82	0.036
5	MTRR	ENSG00000124275.10	rs4143882	0.42	0.029	0.82	0.036
5	FASTKD3	ENSG00000124279.7	rs4143882	0.43	0.025	0.79	0.032
18	FHOD3	ENSG00000134775.11	rs1057251	0.56	-0.067	-0.59	0.11
18	FHOD3	ENSG00000134775.11	rs12455842	0.56	-0.066	-0.58	0.11
18	FHOD3	ENSG00000134775.11	rs12457919	0.56	-0.068	-0.59	0.12
20	SPATA2	ENSG00000158480.6	rs686237	0.59	0.017	0.54	0.031
18	SLC39A6	ENSG00000141424.8	rs12457919	0.67	0.029	0.43	0.066
18	SLC39A6	ENSG00000141424.8	rs1057251	0.68	0.028	0.42	0.066
18	SLC39A6	ENSG00000141424.8	rs12455842	0.68	0.027	0.41	0.066
18	RPRD1A	ENSG00000141425.13	rs12457919	0.74	0.02	0.33	0.061
18	RPRD1A	ENSG00000141425.13	rs1057251	0.75	0.02	0.32	0.061
18	RPRD1A	ENSG00000141425.13	rs12455842	0.75	0.019	0.32	0.061

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20	RNF114	ENSG00000124226.7	rs686237	0.81	-0.013	-0.24	0.054
20	RNF114	ENSG00000124226.7	rs686237	0.81	-0.013	-0.24	0.054
5	C5orf49	ENSG00000215217.2 not sufficiently expressed	rs4143882	NA	NA	NA	NA
5	C5orf49	ENSG00000215217.2 not sufficiently expressed	rs6886921	NA	NA	NA	NA
5	C5orf49	ENSG00000215217.2 not sufficiently expressed	rs727432	NA	NA	NA	NA
11	DLG2	ENSG00000150672.12 not sufficiently expressed	rs963146	NA	NA	NA	NA
18	MOCOS	ENSG00000075643.5 not sufficiently expressed	rs1057251	NA	NA	NA	NA
18	MOCOS	ENSG00000075643.5 not sufficiently expressed	rs12455842	NA	NA	NA	NA
18	MOCOS	ENSG00000075643.5 not sufficiently expressed	rs12457919	NA	NA	NA	NA
20	Gene not found	SI1 not found	rs686237	NA	NA	NA	NA

399 *Significant at the 5% FDR level correction for multiple testing.

Table E12. Association between NO₂ exposure levels at 16 years of age and peripheral blood gene expression levels at 16 years of age in BAMSE (n=243).

Chr	Gene	Probe	Associated SNP	Coef	p-value
5	<i>ADCY2</i>	TC05000054.hg.1	rs6886921	0.032	0.021
5	<i>ADCY2</i>	TC05000055.hg.1	rs6886921	0.023	0.372
11	<i>DLG2</i>	TC11002159.hg.1	rs963146	0.028	0.046
18	<i>MOCOS</i>	TC18000149.hg.1	rs1057251	0.041	0.009
20	<i>B4GALT5</i>	TC20000928.hg.1	rs686237	-0.043	0.194
20	<i>SLC9A8</i>	TC20000391.hg.1	rs686237	-0.023	0.258

Analyses were adjusted for age, sex and cell count. Coef: log fold change in gene expression per 10 µg/m³ increase in NO₂ exposure; p-value: p-value for association between NO₂ exposure and gene expression.

Table E13. Associations between SNP and CpG site methylation (cis-methQTL) at 8 yrs in BAMSE (n=460) with lowest ten p-values.

Chr	GWIS locus	SNP	SNP position		Probe position		beta	se	p-value
			(build 37)	Probe	(build 37)	CpG site location			
5	<i>ADCY2</i>	rs727432[T]	7,663,078	cg02602541	7,850,438	<i>C5orf49</i> (Body)	0.0016	0.0006	0.0071
5	<i>ADCY2</i>	rs4143882[A]	7,664,364	cg02602541	7,850,438	<i>C5orf49</i> (Body)	0.0016	0.0006	0.0085
5	<i>ADCY2</i>	rs727432[T]	7,663,078	cg00984474	7,850,922	<i>C5orf49</i> (Body)	-0.0015	0.0006	0.014
5	<i>ADCY2</i>	rs4143882[A]	7,664,364	cg00984474	7,850,922	<i>C5orf49</i> (Body)	-0.0014	0.0006	0.017
5	<i>ADCY2</i>	rs6886921[T]	7,718,539	cg02602541	7,850,438	<i>C5orf49</i> (Body)	0.0014	0.0006	0.016
11	<i>DLG2</i>	rs963146[G]	83,745,796	cg08432013	83,393,570	<i>DLG2</i> (Body;TSS200)	-0.0060	0.0021	0.0045
11	<i>DLG2</i>	rs963146[G]	83,745,796	cg14716968	84,635,906	<i>DLG2</i> (TSS1500;Body)	-0.0089	0.0034	0.0086
20	<i>B4GALT5</i>	rs686237[A]	48,370,734	cg12058372	48,252,667	<i>B4GALT5</i> (3'UTR)	-0.0060	0.0021	0.0042
20	<i>B4GALT5</i>	rs686237[A]	48,370,734	cg27403406	48,325,721	<i>B4GALT5</i> (Body)	0.0071	0.0028	0.011
20	<i>B4GALT5</i>	rs686237[A]	48,370,734	cg02003117	48,428,318	<i>SLC9A8</i> (TSS1500)	-0.0033	0.0014	0.021

Adjusted for age at the 8 years follow-up, sex, environmental tobacco smoke exposure during first year of life, NO₂ exposure at birth, municipality, cell type, batch (bisulfite treatment date), and asthma up to 8 years of age. No significant methQTLs were detected at the 5% FDR correction level for multiple testing. Chr, chromosome; SNP, using the major allele as reference with a change in beta for each extra minor allele (minor allele in brackets); Beta, CpG site methylation change per additional minor allele; se, standard error.

410 **Table E14.** Human Protein Atlas protein expression profile of genes in normal respiratory system (lung) and smooth muscle tissue.

		Nasopharynx respiratory epithelial cells		Bronchus respiratory epithelial cells		Lung pneumocytes		Lung macrophages		Smooth muscle tissue	
Chr	GWIS locus	Antibody Staining*	Annotated expression	Antibody staining	Annotated expression	Antibody staining	Annotated expression	Antibody staining	Annotated expression	Antibody staining	Annotated expression
5	<i>ADCY2</i>	1-medium, 2-medium, 3-medium,	medium	1-medium, 2-medium, 3-medium	Medium	1-low, 2-medium, 3-low	low	1-medium, 2-medium, 3-high	medium	1-medium, 2-medium, 3-low	medium
11	<i>DLG2</i>	1-low	-	1-medium	-	1-ND	-	1-low	-	ND	-
18	<i>MOCOS</i>	1-medium, 2-ND	medium	1-medium, 2-low	Medium	1-ND, 2-ND	ND	1-low, 2-ND	low	1-high 2-ND	high
20	<i>B4GALT5</i>	NA	-	NA	-	NA	-	NA	-	NA	-

411 ND, not detected; NA, no antibodies available. *Number of antibodies according to Human Protein Atlas (E38).

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