Air pollution drives development of asthma, but not rhinoconjunctivitis throughout childhood and adolescence

Ulrike Gehring, PhD[1], Alet Wijga, PhD[2], Gerard Hoek, PhD[1], Prof. Tom Bellander, PhD[3,4], Prof. Dietrich Berdel, MD[5], Irene Brüske, MD[6], Elaine Fuertes, PhD[6], Olena Gruzieva, PhD[3], Joachim Heinrich, PhD[6], Prof. Barbara Hoffmann, MD, MPH[7,8], Prof. Johan C. de Jongste, MD, PhD[9], Prof. Claudia Klümper, PhD[7], Prof. Gerard H. Koppelman, MD, PhD[10,11], Michal Korek, MSc[3], Prof. Ursula Krämer, PhD[6], Dieter Maier, PhD[12], Erik Melén, MD[3,13], Prof. Göran Pershagen, MD, PhD[3,4], Prof. Dirkje S. Postma, PhD[11,14], Marie Standl, PhD[6], Andrea von Berg, MD[5], Prof. Josep M. Anto, PhD[15,16,17,18], Prof. Jean Bousquet, MD[19], Prof. Thomas Keil, MD[20,21], Prof. Henriette A. Smit, PhD[22], Prof. Bert Brunekreef, PhD[1,22]

[1] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

[2] Center for Nutrition, Prevention and Health Service, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

[3] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[4] Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden

[5] Research Institute, Department of Pediatrics, Marien-Hospital-Wesel, Wesel, Germany

[6] Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

[7] IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

[8] Medical Faculty, Deanery of Medicine, Heinrich-Heine-University of Düsseldorf, Düsseldorf, Germany

[9] Department of Pediatrics, Division of Respiratory Medicine, Erasmus University Medical Center/Sophia Children's Hospital, Rotterdam, The Netherlands

[10] University of Groningen, University Medical Center Groningen, Department of Pediatric Pulmonology, Beatrix Children's Hospital, Groningen, The Netherlands

[11] Groningen Research Institute for Asthma and COPD, University of Groningen, Groningen, The Netherlands

[12] Biomax Informatics AG, Planegg, Germany

[13] Sachs'Children's Hospital, Stockholm, Sweden

[14] University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases, Groningen, The Netherlands

[15] Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

[16] IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

[17] Universitat Pompeu Fabra (UPF), Barcelona, Spain

[18] CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

[19] University Hospital of Montpellier, Hôpital Arnaud de Villeneuve, Montpellier, France

[20] Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany

[21] Institute for Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany

[22] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands

Corresponding author

Ulrike Gehring, PhD
Institute for Risk Assessment Sciences, Utrecht University
P.O. Box 80178, 3508 TD Utrecht, The Netherlands
Phone: +31 (0)30 253 9486, Fax: +31 (0)30 253 9499, Email: u.gehring@uu.nl

Key words: air pollution, asthma, birth cohort, incidence, prevalence, rhinoconjunctivitis

Word count abstract: 246

Word count introduction-conclusions: 3,194

Abstract

Background: The role of air pollution exposure in the development of childhood and adolescent asthma and rhinoconjunctivitis is still unclear. We investigated the longitudinal associations of air pollution exposure with asthma and rhinoconjunctivitis from birth until age 14-16 years.

Methods: For 14,126 participants of four prospective birth cohort studies from Germany, Sweden and The Netherlands, repeated questionnaire-reports of asthma and rhinoconjunctivitis were linked with annual average air pollution concentrations [nitrogen dioxide (NO_2), particulate matter (PM) smaller than 2·5, smaller than 10, and between 2·5 and 10 µm ($PM_{2·5}$, PM_{10}, and PM_{coarse}, respectively), and $PM_{2·5}$ absorbance (indicator of soot)] at the participants' home addresses. Associations of exposure at the birth address and at the address at the time of follow-up with asthma and rhinoconjunctivitis incidence and prevalence were analysed in cohort-specific analyses with subsequent meta-analysis and pooled analyses.

Findings: Overall, the risk of incident asthma until age 14-16 years increased with increasing exposure to NO_2 and "soot" at the birth address [e.g. adjusted meta-analysis odds ratio (95% confidence interval) 1·13 (1·02-1·25) per 10 µg/m^3 NO_2 and 1·29 (1·00-1·66) per 1 unit increase in "soot" exposure, respectively]. A similar trend was observed for $PM_{2·5}$. These associations with asthma were more consistent after the age of 4 years than before that age likely due to more reliable diagnosis. We found no indication for an adverse effect of air pollution on rhinoconjunctivitis.

Interpretation: Air pollution exposure early in life may contribute to the development of asthma throughout childhood and adolescence.

Funding: The European Union

Introduction

Mechanistic support of a causal role of ambient air pollution in the development of asthma and allergic rhinoconjunctivitis is strong.[1] Evidence from prospective cohort studies suggests a causal role of ambient air pollution in the development of childhood asthma is suggestive, e.g.[1,2] but is less clear for allergic rhinoconjunctivitis.[1]

Most of the published analyses focus on the effect of traffic-related air pollution and asthma and rhinoconjunctivitis through early and middle childhood. A Dutch birth cohort reported positive associations between early life air pollution exposure and asthma incidence and prevalence during the first eight years of life.[3] At age 12 years, lifetime risks were still elevated.[4] In a Swedish birth cohort, exposure to nitrogen oxides (NO_x) and particulate matter with a diameter of less than 10 µm (PM_{10}) from traffic during the first year of life was positively associated with prevalent and incident asthma at age 12 years, but not at younger ages.[5] In a cohort of young children from California, new-onset asthma was more likely with increasing traffic-related pollution at homes and schools.[6] Particulate matter with a diameter of less than 2.5 µm ($PM_{2.5}$) exposure at birth was associated with increased risk of asthma at age 7 in a cohort from Vancouver.[7] However, no association was found between nitrogen dioxide (NO_2) and particulate matter exposure and asthma prevalence until ages 10-11 in two German[8] and a British birth cohort.[9] Air pollution tended to be positively associated with hay fever until age 12 in the Dutch cohort,[4] but associations with rhinitis prevalence were heterogeneous across study regions of the German cohorts.[8]

Heterogeneity between findings may be partly explained by differences in exposure assessment, health outcome definition and statistical analysis. Multi-cohort analyses with harmonized exposure and health data so far are limited to cross-sectional analyses of

asthma prevalence at specific ages.[10] Moreover, statistical power to assess age-specific associations with air pollutions in individual cohorts, in particular for onset of disease, is often limited by small numbers. Therefore, we harmonized in the framework of the European collaborative MeDALL project (Mechanisms of the Development of ALLergy)[11] data of four European birth cohort studies, for which a standardized air pollution exposure assessment is available. We linked estimated residential air pollution exposures to repeated questionnaire-reports of asthma and rhinoconjunctivitis throughout childhood and adolescence to elucidate relationships of air pollution and onset and presence of disease at different ages.

Materials and Methods

Study population

This study includes four European birth cohort studies designed to study the development of asthma and allergies in Stockholm county, Sweden (BAMSE: Children, Allergy, Environment, Stockholm, Epidemiologic survey[12]); two parts of Germany, the Munich metropolitan area and the North-Western part of North-Rhine Westphalia (Wesel Area), referred to as "South" and "North", respectively (GINIplus: German Infant Nutrition Intervention study – plus influence of pollution and genetics[13] and LISAplus: influence of Life-style related factors on the Immune System and the development of Allergies in childhood - plus the influence of traffic emissions and genetics[14]); and a series of communities in the north, west and centre of the Netherlands (PIAMA: Prevention and Incidence of Asthma and Mite Allergy[15]). Study participants were born between 1994 (BAMSE) and 1999 (LISAplus). More information about study designs and populations is provided in the Supplemental Material. For the present

analysis, all participants with data on at least one of the health outcomes studied and data on air pollution exposure were included (N=14,126). Ethical approval was obtained from the local authorized Institutional Review Boards and written informed consent was obtained from the parents or legal guardians of all participants.

Health outcomes

Information on the children's respiratory health was collected by repeated questionnaires throughout childhood and adolescence (Supplementary Table 1). All cohorts had follow-ups at ages 1, 2, 4, 6-8, 10-12, and 14-16 years. These data were used in the present analysis. For PIAMA, where multiple follow-ups were performed between 6 and 8 years, the 8-year follow-up was used in the main analysis.

Onset (incidence) and presence (prevalence) of asthma from birth until age 14-16 years and rhinoconjunctivitis from age 4 to 14-16 years were the primary outcomes. Asthma was defined as a positive answer to at least two of the three following questions: (1) "Has a doctor ever diagnosed asthma in your child?", (2) "Has your child had wheezing or whistling in the chest in the last 12 months?", (3) "Has your child been prescribed asthma medication during the last 12 months?". Rhinoconjunctivitis was defined as positive answers to the following two questions: (1) "Has your child been sneezing or did he/she have a runny/blocked nose when he/she did not have a cold during the past 12 months?", (2) "If yes, were the nose symptoms accompanied by itchy, watering eyes?". These definitions have been developed by a panel of experts within the MeDALL consortium.[16]

At 4-6, 8-10, and 12-16 years, blood samples were taken from sub-populations for measurements of specific immunoglobulin (Ig) E levels against common aero allergens

(Supplementary Table 2). Allergic sensitization was defined as a specific IgE level of ≥0·35 IU/mL to one or more of these allergens. Allergic and non-allergic asthma, and allergic rhinoconjunctivitis defined by the presence/absence of allergic sensitization in subgroups of children with measurements of allergen specific IgE were secondary outcomes.

Air pollution exposure assessment

Annual average air pollution concentrations at the participants' birth address and current home address at the different follow-ups were estimated by Land-Use Regression (LUR) models described elsewhere.[17,18] In brief, air pollution monitoring campaigns were performed between October 2008 and February 2010 in each study area. Three two-week measurements of NO_2 were performed within one year at 80 sites in The Netherlands/Belgium and 40 sites in the other areas. Simultaneous measurements of "soot" ($PM_{2·5}$ absorbance, determined as the reflectance of $PM_{2·5}$ filters), $PM_{2·5}$, PM_{10}, and PM_{coarse} (PM_{10}-$PM_{2·5}$) were performed at half of the sites. Results from the three measurements were averaged to estimate the annual average. ENREF 15[18] Predictor variables on nearby traffic, population/household density and land use derived from Geographic Information Systems (GIS) were evaluated to explain spatial variation of annual average concentrations. Regression models (Supplementary Table 3) were developed as described in the Supplemental Material and then used to estimate annual average air pollution concentration at the participants' home addresses, for which the same GIS predictor variables were collected. For GINI/LISA North and South no information was available on exposure at ages 1, 2 and 4, and 1 and 4, respectively. Exposure at the birth and 2-year addresses (GINI/LISA South) was carried forward.

Covariates

Information was collected on important covariates such as sex, parental socio-economic status, native nationality, maternal and paternal asthma and/or hay fever, older siblings, breastfeeding for at least 3 months, maternal smoking during pregnancy; smoking, mold/dampness and furry pets in the child's home, use of natural gas for cooking, and day-care centre attendance. Covariates were defined as similarly as possible across cohorts.

Statistical analysis

Associations of air pollution exposure with asthma and rhinoconjunctivitis incidence from birth until age 14-16 were analysed with discrete-time hazard models,[19] associations with asthma and (allergic) rhinoconjunctivitis prevalence by generalized estimation equations with a logit-link using a 5-dependent/3-dependent/2-dependent correlation matrix, assuming that all observations within the same individual are correlated and that the correlation is the same for all pairs of observations with the same time lag.[20] We pooled data from the GINI and LISA cohorts, as the same procedures were followed in these cohorts, but analysed the two sub-cohorts of the GINI and LISA studies (South and North), separately. Separate analyses were performed with exposure at the birth address and exposure at the address at which a participant lived at the time of the follow-up, taking into account changes in exposure due to changes in address. We analysed associations in two ways: 1) by performing cohort-specific analyses with subsequent random effects meta-analysis,[21] and 2) by pooling data from the various cohorts. We performed all analyses with and without adjustment for the covariates listed above; pooled analyses were additionally adjusted for

cohort. Time-varying confounders were selected from the questionnaire that coincided best with the exposure period. Heterogeneity between cohort-specific effect estimates was evaluated with the I^2 statistic.[22]

We explored in a sensitivity analysis to what extent the results for PIAMA were influenced by using data from selected follow-ups (ages 1, 2, 4, 8, 12 and 14 years) instead of data from all follow-ups (that is yearly follow-ups until age 8, 11 and 14 years). Age- and sex-specific effect estimates were obtained from pooled analyses with exposure-age and exposure-sex interaction terms.

Air pollution levels were entered as continuous variables without transformation in all models. Associations are presented for fixed exposure increments. All analyses were performed with the Statistical Analysis System (SAS 9.2, Cary, NC, USA) for Windows except for meta-analyses, which were performed with Stata (Stata/IC 10.1 for Windows, College Station, TX, USA). Effects are presented as odds ratios with 95% confidence intervals.

Role of the funding source

The funding source had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Population characteristics

Our study sample included 98% the original participants of the BAMSE and PIAMA cohorts and roughly 80% of the original GINI/LISA North and South cohorts. Characteristics of the study population and frequency distributions of health outcomes are presented in Table 1

and Figure 1. More details are provided in the Supplementary Appendix. More than one third of the participants of the BAMSE and PIAMA cohorts and 10-15% of the participants of the GINI and LISA cohorts developed asthma during the follow-up. Roughly, one-quarter to one-third of the participants developed rhinoconjunctivitis during follow-up.

Air pollution exposure

Distributions of exposures at the birth and 14-16 year addresses are presented in Supplementary Table 4. Although more than half of the participants changed address at least once during the follow-up, correlations between exposures at the birth address and at the follow-up addresses were moderate to high (Supplementary Figure 1). Correlations were highest for PIAMA (r=0·61-0·81 for the 14-year addresses) and lowest for BAMSE (r=0·34-0·44 for the 16-year addresses).

Air pollution and health

Overall, after adjustment for potential confounders, the risk of incident asthma until age 14-16 years increased with increasing exposure to NO_2 and $PM_{2.5}$ absorbance at the birth address [adjusted meta-analysis odds ratio (95% confidence interval) 1·13 (1·02-1·25) per 10 $\mu g/m^3$ and 1·29 (1·00-1·66) per 1 unit], but not with exposure at the address at the time of follow-up (Figure 2). Similar associations were found between air pollution exposure and asthma prevalence, but did not reach statistical significance (Figure 3). We found no indication of an adverse effect of air pollution exposure on rhinoconjunctivitis incidence and prevalence (Supplementary Figures 2 and 3).

Changes in associations due to confounder adjustment were generally small (Supplementary Figures 4 and 5). Heterogeneity of cohort-specific effect estimates was low to moderate for asthma and generally moderate to considerable for rhinoconjunctivitis (Supplementary Table 5). Effect estimates from pooled analyses were generally not different from effect estimates of meta-analyses (Supplementary Figures 6 and 7).

When we distinguished between allergic and nonallergic asthma (vs no asthma), associations with air pollution seemed to be limited to non-allergic asthma (Figure 5). Associations with air pollution for allergic rhiniconjunctivitis (Supplementary Figure 8) were similar to associations with all rhinoconjunctivitis.

In analyses with exposure-age interaction terms we found that exposure to NO_2, $PM_{2.5}$ absorbance and $PM_{2.5}$ at the birth address was consistently associated with increased asthma incidence and prevalence after the age of 4 years (Figures 4 and S9). Between 0 to 4 years of age, the picture was mixed. Age-specific associations of exposures at the current address with asthma, like overall associations, were less often statistically significant than associations with exposures at the birth address (Supplementary Figures 10 and 11). For rhinoconjunctivitis, little variation of associations with air pollution exposure with age was found (Supplementary Figures 12 and 13).

Sensitivity analyses

While the positive overall associations between air pollution and asthma prevalence and incidence were largely determined by PIAMA (Supplementary Table 6), the positive associations with air pollution after the age of 4 were also observed in the other cohorts (Supplementary Figures 14 and 15).

Associations of air pollution exposure with health outcomes in PIAMA were basically unchanged when we included information from all follow-ups until age 14 years instead of information from the common follow-up ages with the other cohorts only (Supplementary Figures 16 and 17).

Associations with air pollution tended to be stronger in boys than in girls for asthma, but differences were neither statistically significant nor clinically relevant; we observed no clear trend for rhinoconjunctivitis (Supplementary Figures 18 and 19).

Discussion

This study within four large prospective birth cohort studies with 14-16 years of follow-up provides evidence for positive associations of exposure to NO_2 and $PM_{2.5}$ absorbance early in life with incidence and prevalence of asthma, but not rhinoconjunctivitis throughout childhood and adolescence. The adverse effects of air pollution on asthma incidence and prevalence were more consistent after the age of 4 years than before that age.

The present work is a major extension of previous collaborative work regarding air pollution and asthma within the same cohorts[9]: longitudinal analyses were performed instead of cross-sectional analyses, making full use of the repeated measurements; associations were studied with incidence in addition to prevalence; the follow-up was extended to age 14-16 years; and pooled analyses in addition to cohort-specific analyses with subsequent meta-analyses were performed, resulting in particular in more precise estimates of age-specific effects. Our finding of an increase in asthma incidence with increasing levels of air pollution confirms earlier findings from other cohorts.[6,23-25] The somewhat stronger associations with early life exposure compared to more recent exposure and the more consistent associations

with asthma incidence after the age of 4 confirm earlier findings from the Swedish and Dutch cohorts.[3,5] A similar pattern of inverse associations of NO_2 with onset of asthma before age four and positive associations thereafter, albeit non-significant, was observed in a Norwegian cohort of 9-10-year olds.[26] However, significant positive associations between air pollution and asthma development until age 3-4 were found in a Canadian birth cohort.[25] Most other studies did not differentiate pre-school from school-age onset of asthma. The more consistent associations after the age of 4 years may be explained by the fact that young children are difficult to diagnose with asthma,[27] making outcome misclassification more of a concern during the first four years of life than thereafter. Misclassification is likely non-differential, i.e. not related to air pollution exposure, biasing effects towards the null. Diagnostic conventions for asthma are different in the countries of the four cohorts. Since only a minority of children with reports of symptoms in early childhood develops asthma at school-age[27] German paediatricians, for example are cautious to label a pre-school aged child as asthmatic,[28] which seems not to be the case for Swedish and Dutch paediatricians. This may explain differences in asthma frequencies before the age of 4 years between cohorts. Asthma incidence reported from other cohorts within the same age range, e.g.[24-26] were between the incidence in the German cohorts and the incidence in the Dutch and Swedish cohorts. The degree of outcome misclassification is unknown and we cannot rule out that it differs between cohorts.

Oxidative stress, triggering inflammation is thought to be the main mechanism behind the association between ambient air pollution and asthma.[1] Only few studies so far distinguished allergic from non-allergic asthma. The stronger associations with non-allergic asthma than with allergic asthma confirm earlier findings of the Swedish and Dutch cohorts.[3,5] A cohort study from California investigated air pollution effects in strata of

children with and without a history of allergic symptoms and found stronger effects in children with no allergic symptoms.[29] It has been suggested that the effects of air pollution exposure on non-allergic asthma may be explained by increased non-allergic inflammation.[30]

The inconsistency of the cohort-specific effect estimates together with the overall lack of an association between air pollution and rhinoconjunctivitis is in line with the lack of association between air pollution and allergic sensitization at ages 4 and 8 years in a recent analysis.[31] Moreover, our finding supports the conclusions of a recent review.[1]

Asthma was associated with exposure to NO_2 and $PM_{2.5}$ absorbance. We could not disentangle the effects of these pollutants that share combustion engines as a major source because of the high correlation. This is a limitation of population studies investigating long-term air pollution effects under real-life conditions. However, there is also merit in quantifying joint effects of air pollution mixtures.[32] It has been previously suggested that NO_2 merely acts as a surrogate for a complex mix of air pollution, a recent review, however, concluded that NO_2 individually or in combination with other pollutants is likely to cause adverse health effects.[33] No consistent associations were found with particle mass ($PM_{2.5}$, PM_{10} and PM_{coarse}) possibly due to the generally worse performance of the LUR models for particle mass.

The large sample size, the length of the follow-up from birth through adolescence, the standardized exposure assessment together with the harmonization of outcome and confounder data between cohorts, and the pooling of cohort-specific datasets are important strengths of our study. A limitation of our study might be that we used exposure models based on air pollution measurement campaigns performed in 2008-2010 to assess exposure to air pollution for the entire follow-up. While the measurement campaigns coincided with

the most recent follow-ups of the cohorts, this could be problematic for assessing historical exposures. Our assumption of the spatial contrasts in air pollution levels being unchanged through the years of follow-up is supported by studies from Europe suggesting stable spatial contrasts of NO_2 and black carbon over periods of seven and more years,[34-36] By using purely spatial LUR models in the analyses with more recent exposure, we did not account for long-term trends in air pollution levels. In the Stockholm area (BAMSE), but not in the other study areas, NO_2 and $PM_{2.5}$ levels decreased by about 30% from 1999 to 2009.[37,38] This may have biased associations with more recent exposure, but is no concern for analyses with early life exposures that solely rely on spatial contrasts within cohorts. The fact that we solely relied on residential exposures and did not include exposure at locations other than home and/or time-activity pattern may be another limitation of our study. During preschool years, this is more of a concern for the Swedish and Dutch cohorts, where day-care attendance is common. At school age, the impact is likely the same for all cohorts. High correlations between home and school exposures have been reported from the Swedish and Dutch cohorts,[39,40] and measurement error resulting from relying on residential exposure only is likely non-differential. Spatial clustering and confounding of associations by area-level socio-economic status have been explored in the framework of previous analyses within the same cohorts and have not been found.[e.g.10,31] In our study sample children of atopic parents and children of highly educated parents were overrepresented. Since the results were largely unchanged by adjustment for potential cofounders including parental atopy and parental education, this most likely did not influence our results.

Conclusions

Air pollution exposure early in life may contribute to the development of asthma throughout childhood and adolescence.

Panel: Research in context

Evidence before this study

Before the start of this study, there was suggestive evidence from prospective cohort studies for a causal role of ambient air pollution in the development of childhood asthma. The role of ambient air pollution in the development of allergic rhinoconjunctivitis was even less clear. The studies that have been performed so far differ with regard to exposure assessment, health outcome definition and statistical analysis, which may explain part of the heterogeneity in study findings. Recently, cohort-specific cross-sectional analyses with subsequent meta-analyses of the relationship between air pollution and asthma prevalence, but not incidence, at specific ages were performed in five European cohorts with harmonized exposure and health data.[9] Age-specific associations with air pollution have been studied in single cohorts, but in particular for onset of disease, statistical power is low.

Added values of this study

For the first time, we were able to pool data from four large prospective birth cohort studies. We included data from repeated follow-ups until age 14-16 years and made full use of these data by performing longitudinal analyses instead of cross-sectional analyses. We studied associations with incidence in addition to prevalence and estimated overall as well as age-specific effects.

Implications of all the available evidence

We found adverse effects of exposure to air pollution early in life on asthma incidence and prevalence, in particular after the age of 4 years, when asthma can be more reliably diagnosed. Our results strengthen the evidence for ambient air pollution contributing to the development of asthma in children and adolescents and suggest that reductions in air pollution levels could help to prevent the development of asthma in children.

Authors'contributions

UG designed the study, had full access to all the data in the study, carried out the statistical analysis, wrote the initial draft and had final responsibility for the decision to submit for publication. UG en DM prepared the common database, EM, OG (BAMSE), JH, EF, MS, IB, BH, CK, DB, AvB, UK (GINIplus and LISAplus), and UG, AHW, HAS, JCdJ (PIAMA) provided data. JB, JMA and TK secured funding. BB, GH, TB, MK, GP, EF contributed to the air pollution exposure assessment. All authors (i) provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, (ii) revised the manuscript for important intellectual content, (iii) approved the final version, and (iv) agreed to be accountable for all aspects of the work.

Conflicts of interest

Professor Gerard H. Koppelman reports grants from TEVA outside the submitted work. The University of Groningen has received money for Professor Dirkje S. Postma regarding an

unrestricted educational grant for research from Astra Zeneca and Chiesi. Travel to ERS and/or ATS has been partially funded by Astra Zeneca, Chiesi, Glaxo Smith Kline, and Nycomed. Fees for consultancies were given to the University of Groningen by Astra Zeneca, Ingelheim Boehringer, Chiesi, GSK, Nycomed, and TEVA. Travel and lectures in China were paid to Professor Dirkje S Postma by Chiesi. Professor Jean Bousquet reports personal fees outside the submitted work from Actelion, Almirall, Meda, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach for advisory board membership; from Almirall, AstraZeneca, Chiesi, Glaxo Smith Kline, Meda, Merck, MSD, Novartis, OM Pharma, Sanofi-Aventis, Schering Plough, Takeda, Teva, and Uriach for lectures during meetings; and from Stallergènes for board of directors membership.The other authors declare no conflict of interest.

Acknowledgements

We would like to thank all families participating in the BAMSE, GINIplus and LISAplus and PIAMA cohort studies, and the respective study teams for their hard work and effort.

The research leading to these results has received funding from the European Community's Seventh Framework Program under grant agreement numbers 261357 (MeDALL) and 211250 (ESCAPE). The BAMSE study was supported by the Swedish Research Council FORMAS, the Stockholm County Council, the Swedish Heart and Lung Foundation, the Swedish Foundation for Health Care Sciences and Allergy Research, the Swedish Research Council, and the Swedish Environmental Protection Agency. The GINIplus study was mainly supported for the first 3 years of the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum Munich (former GSF) (observational

arm). The 4 year, 6 year, and 10 year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centres (Helmholtz Zentrum Munich (former GSF), Marien-Hospital Wesel, LMU Munich, TU Munich and from 6 years onwards also from IUF – Leibniz Research-Institute for Environmental Medicine) and a grant from the Federal Ministry for Environment (IUF, FKZ 20462296). The LISAplus study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research – UFZ, Leipzig, Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4 year, 6 year, and 10 year follow-up examinations of the LISAplus study were covered from the respective budgets of the involved partners (Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research – UFZ, Leipzig, Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF – Leibniz-Research Institute for Environmental Medicine) and in addition by a grant from the Federal Ministry for Environment (IUF, FKZ 20462296). The PIAMA study is supported by The Netherlands Organization for Health Research and Development; The Netherlands Organization for Scientific Research; The Netherlands Asthma Fund; The Netherlands Ministry of Spatial Planning, Housing, and the Environment; and The Netherlands Ministry of Health, Welfare, and Sport.

References

1. Health Effects Institute (HEI) Panel on the Health Effects of Traffic-Related Air Pollution.. Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects. Boston, Massachusetts, USA: Health Effects Institute; 2010.
2. Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy*. 2015; **70**(3): 245-56.
3. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M, et al. Traffic-Related Air Pollution and the Development of Asthma and Allergies During The First 8 Years of Life. *Am J Respir Crit Care Med*. 2010; **181**(6): 596-603.
4. Gehring U, Beelen R, Eeftens M, Hoek G, de Hoogh K, de Jongste JC, et al. Particulate matter composition and respiratory health: the PIAMA Birth Cohort study. *Epidemiology*. 2015; **26**(3): 300-9.
5. Gruzieva O, Bergstrom A, Hulchiy O, Kull I, Lind T, Melen E, et al. Exposure to air pollution from traffic and childhood asthma until 12 years of age. *Epidemiology*. 2013; **24**(1): 54-61.
6. McConnell R, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F, et al. Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect*. 2010; **118**(7): 1021-6.
7. Carlsten C, Ferguson A, Dimich-Ward H, Chan H, DyBuncio A, Rousseau R, et al. Association between endotoxin and mite allergen exposure with asthma and specific

sensitization at age 7 in high-risk children. *Pediatr Allergy Immunol*. 2011; **22**(3): 320-6.

8. Fuertes E, Standl M, Cyrys J, Berdel D, von Berg A, Bauer CP, et al. A longitudinal analysis of associations between traffic-related air pollution with asthma, allergies and sensitization in the GINIplus and LISAplus birth cohorts. *PeerJ*. 2013; **1**: e193.
9. Molter A, Agius R, de Vocht F, Lindley S, Gerrard W, Custovic A, et al. Effects of long-term exposure to PM10 and NO2 on asthma and wheeze in a prospective birth cohort. *J Epidemiol Community Health*. 2014; **68**(1): 21-8.
10. Molter A, Simpson A, Berdel D, Brunekreef B, Custovic A, Cyrys J, et al. A multicentre study of air pollution exposure and childhood asthma prevalence: the ESCAPE project. *Eur Respir J*. 2015; **45**(3): 610-24.
11. Bousquet J, Anto J, Auffray C, Akdis M, Cambon-Thomsen A, Keil T, et al. MeDALL (Mechanisms of the Development of ALLergy): an integrated approach from phenotypes to systems medicine. *Allergy*. 2011; **66**(5): 596-604.
12. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol*. 2002; **13 Suppl 15**: 11-3.
13. von Berg A, Kramer U, Link E, Bollrath C, Heinrich J, Brockow I, et al. Impact of early feeding on childhood eczema: development after nutritional intervention compared with the natural course - the GINIplus study up to the age of 6 years. *Clin Exp Allergy*. 2010; **40**(4): 627-36.
14. Heinrich J, Bolte G, Hölscher B, Douwes J, Lehmann I, Fahlbusch B, et al. Allergens and endotoxin on mothers' mattresses and total immunoglobuline E in cord blood of neonates. *Eur Respir J*. 2002; **20**: 617-23.

15. Wijga AH, Kerkhof M, Gehring U, de Jongste JC, Postma DS, Aalberse RC, et al. Cohort profile: the prevention and incidence of asthma and mite allergy (PIAMA) birth cohort. *Int J Epidemiol*. 2014; **43**(2): 527-35.

16. Pinart M, Benet M, Annesi-Maesano I, von Berg A, Berdel D, Carlsen KC, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. *Lancet Respir Med*. 2014; **2**(2): 131-40.

17. Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe - The ESCAPE project. *Atmos Environ*. 2013; **72**: 10-23.

18. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. Development of Land Use Regression Models for PM2.5, PM2.5 Absorbance, PM10 and PMcoarse in 20 European Study Areas; Results of the ESCAPE Project. *Environ Sci Technol*. 2012; **46**(20): 11195-205.

19. Singer JD, Willett JB. Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. New York: Oxford University Press; 2003.

20. Diggle PJ, Liang KY, Zeger SL. Analysis of longitudinal data. Oxford: Clarendon Press; 1994.

21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; **7**(3): 177-88.

22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; **21**(11): 1539-58.

23. Shima M, Nitta Y, Ando M, Adachi M. Effects of air pollution on the prevalence and incidence of asthma in children. *Arch Environ Health*. 2002; **57**(6): 529-35.

24. Jerrett M, Shankardass K, Berhane K, Gauderman WJ, Kunzli N, Avol E, et al. Traffic-Related Air Pollution and Asthma Onset in Children: A Prospective Cohort Study with Individual Exposure Measurement. *Environ Health Perspect*. 2008; **116** (10): 1433-8.

25. Clark NA, Demers PA, Karr CJ, Koehoorn M, Lencar C, Tamburic L, et al. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect*. 2010; **118**(2): 284-90.

26. Oftedal B, Nystad W, Brunekreef B, Nafstad P. Long-term traffic-related exposures and asthma onset in schoolchildren in oslo, norway. *Environ Health Perspect*. 2009; **117**(5): 839-44.

27. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995; **332**(3): 133-8.

28. Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der, (AWMF) WMF. Nationale VersorgungsLeitlinie Asthma - Langfassung, 2. Auflage.Version 5. 2009, zuletzt geändert: August 2013. Available from:http://www.versorgungsleitlinien.de/themen/asthma, accessed June 4, 2015; 2013.

29. McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, et al. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect*. 2006; **114**(5): 766-72.

30. World Health Organization (WHO) Regional Office for Europe. Health effects of transport-related air pollution. Copenhagen: WHO Regional Office for Europe

(http://www.euro.who.int/__data/assets/pdf_file/0006/74715/E86650.pdf accessed September 18, 2015); 2005.

31. Gruzieva O, Gehring U, Aalberse R, Agius R, Beelen R, Behrendt H, et al. Meta-analysis of air pollution exposure association with allergic sensitization in European birth cohorts. *J Allergy Clin Immunol*. 2014; **133**(3): 767-76 e7.

32. Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, et al. Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med*. 2013; **188**(5): 593-9.

33. World Health Organization (WHO) Regional Office for Europe. Review of evidence on health aspects of air pollution - REVIHAAP Project. Copenhagen, Denmark: WHO Regional Office for Europe (http://www.euro.who.int/__data/assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report-final-version.pdf accessed June 4, 2015); 2013.

34. Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G. Stability of measured and modelled spatial contrasts in NO(2) over time. *Occup Environ Med*. 2011; **68**(10): 765-70.

35. Cesaroni G, Porta D, Badaloni C, Stafoggia M, Eeftens M, Meliefste K, et al. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health*. 2012; **11**: 48.

36. Gulliver J, Morris C, Lee K, Vienneau D, Briggs D, Hansell A. Land Use Regression Modeling To Estimate Historic (1962-1991) Concentrations of Black Smoke and Sulfur Dioxide for Great Britain. *Environ Sci Technol*. 2011; **45**(8): 3526-32.

37. Durant JL, Beelen R, Eeftens M, Meliefste K, Cyrys J, Heinrich J, et al. Comparison of ambient airborne PM(2).(5), PM(2).(5) absorbance and nitrogen dioxide ratios

measured in 1999 and 2009 in three areas in Europe. *Sci Total Environ*. 2014; **487**: 290-8.

38. Klumper C, Kramer U, Lehmann I, von Berg A, Berdel D, Herberth G, et al. Air pollution and cytokine responsiveness in asthmatic and non-asthmatic children. *Environ Res*. 2015; **138**: 381-90.

39. Gruzieva O, Bellander T, Eneroth K, Kull I, Melen E, Nordling E, et al. Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. *J Allergy ClinImmunol*. 2012; **129**(1): 240-6.

40. Bilenko N, van Rossem L, Brunekreef B, Beelen R, Eeftens M, Hoek G, et al. Traffic-related air pollution and noise and children's blood pressure: results from the PIAMA birth cohort study. *Eur J Prev Cardiol*. 2015; **22**(1): 4-12.

Figure Legends

Figure 1. Prevalence (bars) and cumulative hazard functions (lines) for asthma and rhinoconjunctivitis.

Figure 2. Adjusted [a] cohort specific and combined (meta random) odds ratios of the associations of air pollution exposure with asthma incidence. Black dots represent associations with birth address exposure, white dots represent associations with current address exposure.

[a] adjusted for sex, maternal and paternal asthma and hay fever, native nationality, parental education, breastfeeding, older siblings, day-care attendance, maternal smoking during pregnancy, parental smoking at home, mould/dampness at home, pets, use of gas for cooking, and municipality (BAMSE only)

Figure 3. Adjusted [a] cohort specific and combined (meta random) odds ratios of the associations of air pollution exposure with asthma prevalence. Black dots represent associations with birth address exposure, white dots represent associations with current address exposure.

[a] adjusted for sex, maternal and paternal asthma and hay fever, native nationality, parental education, breastfeeding, older siblings, day-care attendance, maternal

smoking during pregnancy, parental smoking at home, mould/dampness at home, pets, use of gas for cooking, and municipality (BAMSE only)

Figure 4. Adjusted [a] age-specific odds ratios of the associations of air pollution exposure at the birth address with asthma incidence from pooled analyses.

[a] adjusted for maternal and paternal asthma and hay fever, native nationality, parental education, breastfeeding, older siblings, day-care attendance, maternal smoking during pregnancy, parental smoking at home, mould/dampness at home, pets, use of gas for cooking, municipality (BAMSE only), and cohort

Figure 5. Adjusted [a] odds ratios of the associations of air pollution exposure at the birth address with allergic and non-allergic asthma prevalence from pooled analysis. Black dots represent associations for non-allergic asthma, white dots represent associations for allergic asthma.

[a] adjusted for sex, maternal and paternal asthma and hay fever, native nationality, parental education, breastfeeding, older siblings, day-care attendance, maternal smoking during pregnancy, parental smoking at home, mould/dampness at home, pets, use of gas for cooking, municipality (BAMSE only) and cohort