Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study

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Summary

Background **Previous published analyses have focused on the effect of air pollution on asthma and rhinoconjunctivitis throughout early and middle childhood. However, the role of exposure to air pollution in the development of childhood and adolescent asthma and rhinoconjunctivitis remains unclear. We aimed to assess the longitudinal associations between exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence.**

Methods **We did a population-based birth cohort study of 14 126 participants from four prospective birth cohort studies from Germany, Sweden, and the Netherlands with 14–16 years of follow-up. We linked repeated questionnaire reports of asthma and rhinoconjunctivitis with annual average air pollution concentrations (nitrogen dioxide [NO_2], particulate matter [PM] with a diameter of less than 2·5 μm [$PM_{2·5}$], less than 10 μm [PM_{10}], and between 2·5 μm and 10 μm [PM_{coarse}], and $PM_{2·5}$ absorbance [indicator of soot]) at the participants' home addresses. We analysed longitudinal associations of air pollution exposure at participants' birth addresses and addresses at the time of follow-up with asthma and rhinoconjunctivitis incidence and prevalence in cohort-specific analyses, with subsequent meta-analysis and pooled analyses.**

Findings **Overall, the risk of incident asthma up to age 14–16 years increased with increasing exposure to NO_2 (adjusted meta-analysis odds ratio [OR] 1·13 per 10 μg/m³ [95% CI 1·02–1·25]) and $PM_{2·5}$ absorbance (1·29 per 1 unit [1·00–1·66]) at the birth address. A similar, albeit non-significant, trend was shown for $PM_{2·5}$ and incident asthma (meta-analysis OR 1·25 per 5 μg/m³ [95% CI 0·94–1·66]). These associations with asthma were more consistent after age 4 years than before that age. There was no indication of an adverse effect of air pollution on rhinoconjunctivitis.**

Interpretation **Exposure to air pollution early in life might contribute to the development of asthma throughout childhood and adolescence, particularly after age 4 years, when asthma can be more reliably diagnosed. Reductions in levels of air pollution could help to prevent the development of asthma in children.**

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See Online for podcast interview with Ulrike Gehring

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Introduction

Mechanistic support for 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,[1,2] but is less clear for allergic rhinoconjunctivitis.[1]

Most published analyses focus on the effect of traffic-related air pollution on asthma and rhinoconjunctivitis throughout early and middle childhood. Findings from the Dutch PIAMA birth cohort study[3] showed positive associations between exposure to air pollution in early life and asthma incidence and prevalence during the first 8 years of life. At age 12 years, lifetime risks of asthma remained heightened.[4] In the Swedish BAMSE birth cohort,[5] 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 ages 1, 2, 4, and 8 years. In a cohort of young children from California, new-onset asthma was associated with increasing traffic-related pollution at homes and schools.[6] Exposure at birth to particulate matter with a diameter of less than 2·5 μm ($PM_{2·5}$) was associated with an increased risk of asthma at age 7 years in a cohort from Canada.[7] However, no association was shown between nitrogen dioxide (NO_2) or particulate matter exposure and asthma prevalence until age 10–11 years in the German GINIplus and LISAplus cohorts[8] and one British birth cohort.[9] Air pollution tended to be positively associated with hay fever until age 12 years in the PIAMA cohort,[4] but associations with rhinitis prevalence were heterogeneous across study regions of the GINIplus and LISAplus cohorts.[8]

Heterogeneity between findings might be partly explained by differences in exposure assessment, definition of health outcomes, and statistical analysis. Previous multicohort analyses with harmonised exposure

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See Online for appendix

Research in context

Evidence before this study

No systematic review was done as part of the planning for this study. Evidence from prospective cohort studies suggests a causal role of ambient air pollution in the development of childhood asthma, but is less clear for the development of allergic rhinoconjunctivitis. Studies done so far differ with regard to exposure assessment, health outcome definition, and statistical analysis, which might explain part of the heterogeneity in study findings. In the past few years, cohort-specific cross-sectional analyses with subsequent meta-analyses of the association between air pollution and asthma prevalence, but not incidence, at specific ages were undertaken in five European cohorts with harmonised exposure and health data. Age-specific associations with air pollution have been studied in single cohorts, but statistical power is low, particularly for onset of disease.

Added value 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-up assessments up to age 14–16 years and made full use of these data by undertaking longitudinal rather than cross-sectional analyses. We studied associations with incidence in addition to prevalence and estimated both overall and age-specific effects.

Implications of all the available evidence

We recorded 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 the contribution of ambient air pollution to the development of asthma in children and adolescents, and suggest that reductions in levels of air pollution could help to prevent the development of asthma in children.

and health data have been 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 used the framework of the European collaborative Mechanisms of the Development of ALLergy (MeDALL) project[11] to harmonise data for four European birth cohort studies for which a standardised assessment of air pollution exposure is available. We linked estimated residential air pollution exposures to repeated questionnaire reports of asthma and rhinoconjunctivitis throughout childhood and adolescence to elucidate associations between air pollution and onset and presence of disease at different ages.

Methods

Study design and participants

In this population-based birth cohort study, we pooled data of participants from four European birth cohort studies designed to investigate the development of asthma and allergies in Stockholm county, Sweden (BAMSE[12]); two parts of Germany (the Munich metropolitan area and the northwestern part of North Rhine-Westphalia (Wesel area), referred to as South and North, respectively (GINIplus[13] and LISAplus[14]); and a series of communities in the north, west, and centre of the Netherlands (PIAMA[15]). Study participants were born between 1994 (BAMSE) and 1999 (LISAplus). We included all participants with data for at least one of the health outcomes studied and for exposure to air pollution (N=14 126). Appendix p 2 provides additional information about study designs and populations. Ethical approval was obtained from the local authorised Institutional Review Boards. Participants' parents or legal guardians provided written informed consent.

Procedures

Information about participants' respiratory health was obtained via repeated questionnaires throughout childhood and adolescence (appendix p 5). All cohorts were followed up at ages 1, 2, 4, 6–8, 10–12, and 14–16 years; we used these follow-up data in the present analysis. For PIAMA, in which multiple follow-ups were done between ages 6 and 8 years, we used data for the 8 year follow-up.

We estimated annual average air pollution concentrations at participants' birth and current home addresses at the different follow-up visits with land-use regression models, as described elsewhere.[16,17] In brief, air pollution monitoring campaigns were done between October, 2008, and February, 2010, in each study area. Three measurements of NO_2 over a period of 2 weeks were done within 1 year at 80 sites in the Netherlands and 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_{10}–$PM_{2·5}$ (PM_{coarse}) were done at half the sites. Results from the three measurements were averaged to estimate the annual average.[17] We evaluated predictor variables of nearby traffic, population and household density, and land use derived from Geographic Information Systems to explain spatial variation in annual average concentrations. We developed regression models (appendix pp 3, 6, 7), which we used to estimate annual average air pollution concentrations at participants' home addresses, for which the same Geographic Information Systems predictor variables were obtained. For GINI and LISA North, no information was available about exposure at ages 1, 2, and 4 years, and for the South cohort, none was available at ages 1 and 4 years. Exposure at the birth and 2 year addresses (GINI and LISA South) was carried forward.

Outcomes

Our primary outcomes were onset (incidence) and presence (prevalence) of asthma from birth until age 14–16 years and rhinoconjunctivitis from age 4 years to 14–16 years. We defined asthma 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?", and (3) "Has your child been prescribed asthma medication during the last 12 months?". We defined rhinoconjunctivitis 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?", and (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.[18]

At ages 4–6, 8–10, and 12–16 years, blood samples were taken from subpopulations for measurements of specific immunoglobulin (Ig) E concentrations against common aeroallergens (appendix pp 2, 3, 8). We defined allergic sensitisation as a specific IgE concentration of

	BAMSE (N=4010)	GINI and LISA North (N=2691)	GINI and LISA South (N=3558)	PIAMA (N=3867)
Sex				
Female	1979 (49%)	1310 (49%)	1689 (47%)	1864 (48%)
Male	2031 (51%)	1381 (51%)	1869 (53%)	2003 (52%)
Maternal asthma or hay fever	848 (21%)	551/2575 (21%)	1211/3411 (36%)	929/3830 (24%)
Paternal asthma or hay fever	798/3967 (20%)	466/2527 (18%)	1101/3285 (34%)	960/3834 (25%)
Native nationality	2680/3396 (79%)	2416/2433 (99%)	3075/3460 (89%)	3324/3680 (90%)
High maternal education	1642/3983 (41%)	802/2404 (33%)	1937/3184 (61%)	1330/3802 (35%)
High paternal education	1543/3908 (39%)	814/2332 (35%)	2140/3088 (69%)	1492/3756 (40%)
Breastfeeding (≥12 weeks)	3633/3878 (94%)	1660/2555 (65%)	2913/3398 (86%)	1675/3628 (46%)
Older siblings	1934 (48%)	1425/2547 (56%)	1470/3407 (43%)	1943/3865 (50%)
Attendance at a day-care centre*	3197/3825 (84%)	91/2384 (4%)	411/2651 (16%)	2127/3699 (58%)
Mother smoked during pregnancy	513/4009 (13%)	450/2626 (17%)	466/3455 (13%)	669/3834 (17%)
Parents smoking at child's home				
Early life†	835/3988 (21%)	843/2430 (35%)	535/3205 (17%)	955/3810 (25%)
Most recent follow-up‡	412/3023 (14%)	167/1590 (11%)	108/2280 (5%)	184/2333 (8%)
Use of natural gas for cooking				
Early life†	469 (12%)	110/2608 (4%)	270/3488 (8%)	3173/3837 (83%)
Most recent follow-up‡	196/3101 (6%)	82/1732 (5%)	206/2364 (9%)	1789/2330 (77%)
Mould or dampness in child's home				
Early life†	334/3994 (8%)	489/2608 (19%)	937/3483 (27%)	1612/3473 (46%)
Most recent follow-up‡	140/3098 (5%)	190/1731 (11%)	432/2368 (18%)	882/2328 (38%)
Furry pets in home				
Early life†	615 (15%)	703/2578 (27%)	738/3428 (22%)	1976/3853 (51%)
Most recent follow-up‡	1494/3090 (48%)	888/1720 (52%)	1147/2298 (50%)	1435/3328 (62%)
Changed address§	2699/3169 (85%)	840/1770 (47%)	1778/2661 (67%)	1468/2311 (64%)
Allergic asthma				
4–6 years¶	101/2565 (4%)	30/977 (3%)	68/1899 (4%)	40/678 (6%)
8–10 years‖	153/2423 (6%)	38/848 (4%)	92/2560 (4%)	93/1600 (6%)
12–16 years**	172/2499 (7%)	41/943 (4%)	124/2395 (5%)	78/1270 (6%)
Non-allergic asthma				
4–6 years¶	309/2565 (12%)	26/977 (3%)	3/1899 (0%)	44/674 (7%)
8–10 years‖	122/2423 (5%)	30/848 (4%)	23/2560 (1%)	49/1600 (3%)
12–16 years**	74/2499 (3%)	20/943 (2%)	18/2395 (1%)	17/1270 (1%)
Allergic rhinoconjunctivitis				
4–6 years¶	63/2585 (2%)	52/989 (5%)	165/1909 (9%)	26/699 (4%)
8–10 years‖	164/2427 (7%)	82/861 (10%)	326/2570 (13%)	89/1669 (5%)
12–16 years**	338/2516 (13%)	142/968 (15%)	467/2438 (19%)	119/1283 (9%)

Data are n (%) or n/N (%). *During the second year of life for BAMSE, GINI, and PIAMA, and during the third year of life for LISA. †At baseline or during the first year of life if no baseline information available. ‡Age 16 years for BAMSE, age 15 years for GINI and LISA, and age 14 years for PIAMA. §Any change of address between birth and most recent follow-up. ¶Age 4 years in BAMSE and PIAMA, and age 6 years in GINI and LISA. ‖Age 8 years in BAMSE and PIAMA, and age 10 years in GINI and LISA. **Age 16 years in BAMSE, age 15 years in GINI and LISA, and age 12 years in PIAMA.

Table: **Characteristics of the study population**

0·35 kU/mL (1 kU/L=2·4×10³ µg/L) or more to one or more of these allergens. Secondary outcomes were allergic and non-allergic asthma, and allergic rhinoconjunctivitis defined by the presence or absence of allergic sensitisation in subgroups of children with measurements of allergen-specific IgE.

Statistical analysis

We analysed associations of air pollution exposure with asthma from birth, and with rhinoconjunctivitis from age 4 years, to age 14–16 years with discrete-time hazard models,[19] and associations with prevalence of asthma, rhinoconjunctivitis, and allergic rhinoconjunctivitis with

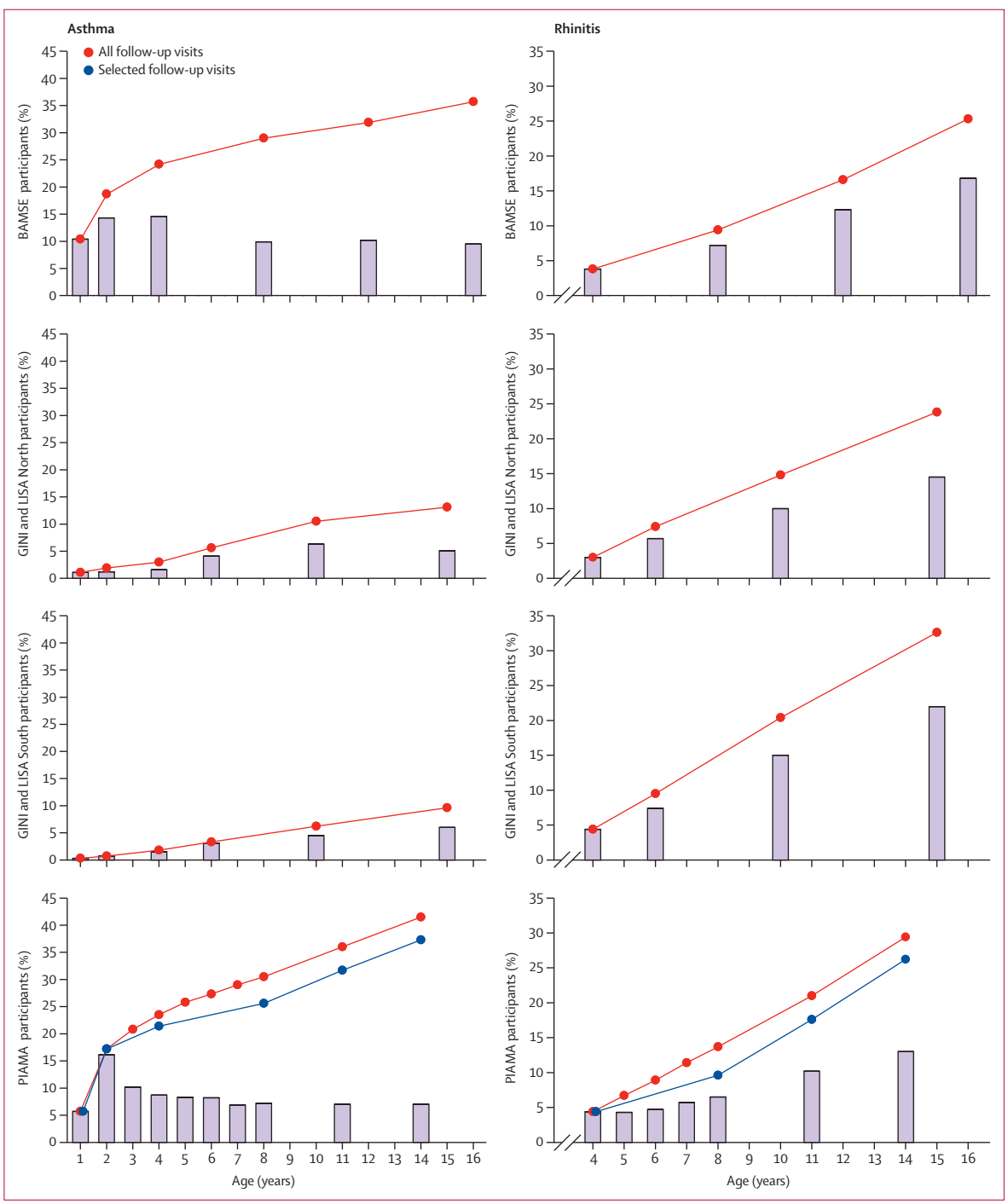

***Figure 1*: Prevalence of asthma and rhinoconjunctivitis in the four birth cohorts**
Lines show cumulative hazard functions.

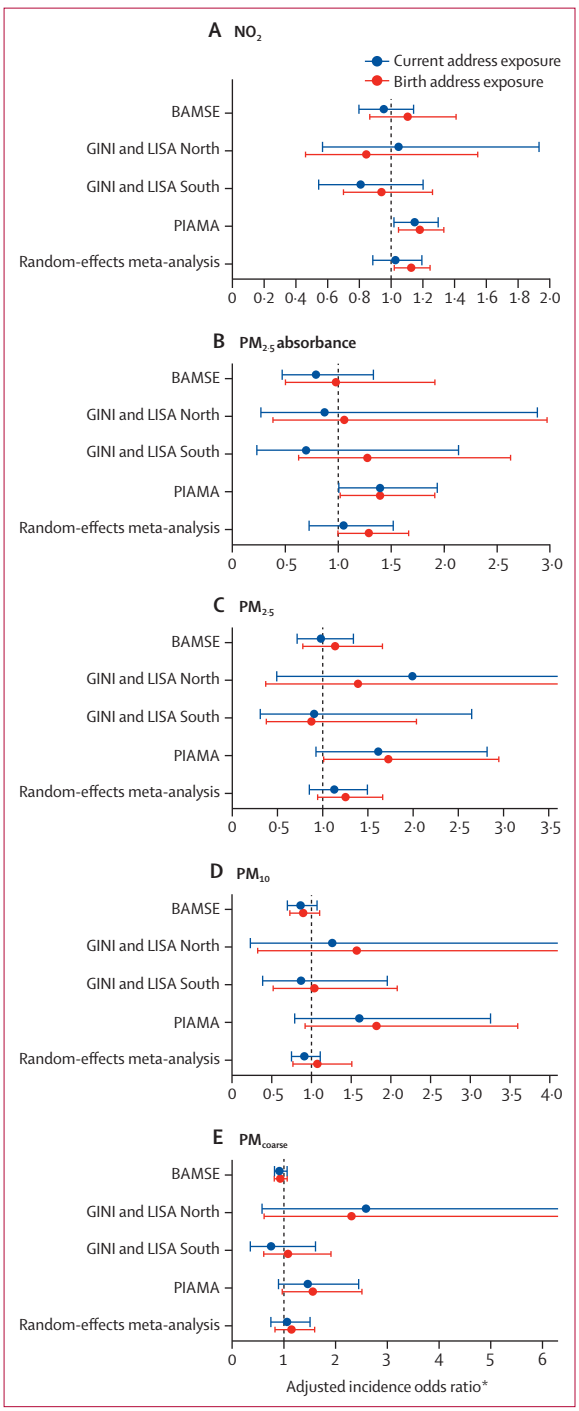

***Figure 2*: Adjusted cohort-specific and combined odds ratios of the associations of air pollution exposure with asthma incidence**
Error bars show 95% CIs. NO_2=nitrogen dioxide. $PM_{2·5}$=particulate matter with a diameter of less than 2·5 μm. PM_{10}=less than 10 μm. PM_{coarse}=particulate matter with a diameter between 2·5 μm and 10 μm. *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 or dampness at home, pets, use of gas for cooking, and municipality (BAMSE only).

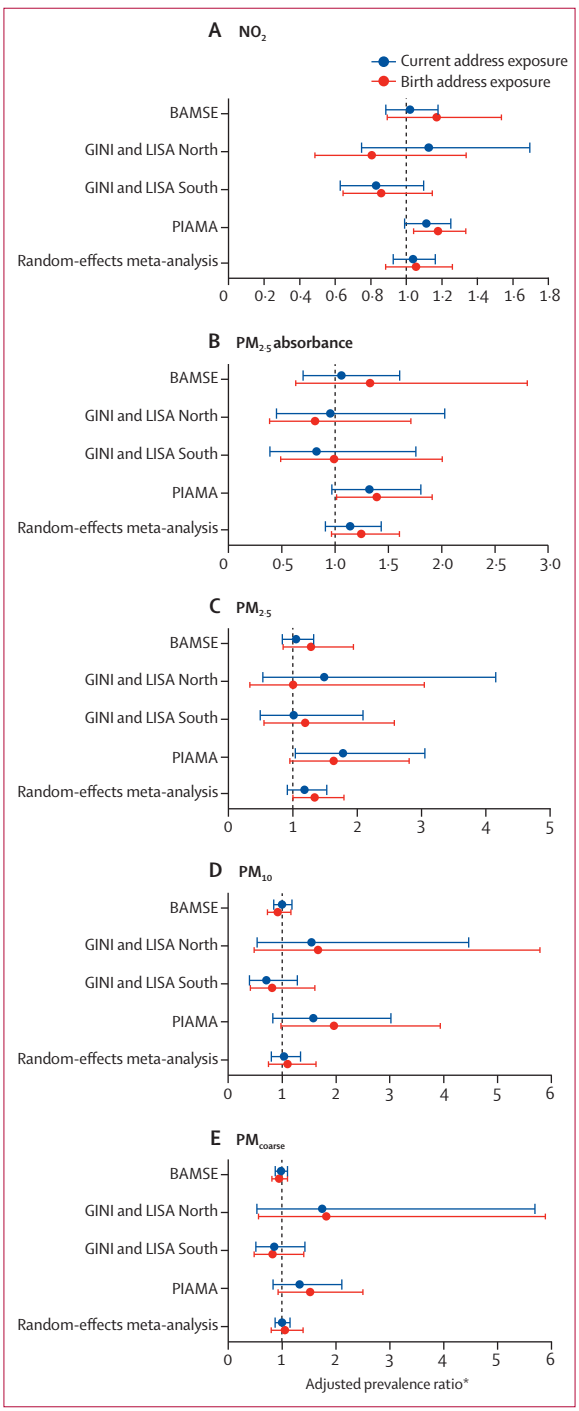

***Figure 3*: Adjusted cohort-specific and combined odds ratios of the associations of air pollution exposure with asthma prevalence**
Error bars show 95% CIs. NO_2=nitrogen dioxide. $PM_{2·5}$=particulate matter with a diameter of less than 2·5 μm. PM_{10}=less than 10 μm. PM_{coarse}=particulate matter with a diameter between 2·5 μm and 10 μm. *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 or dampness at home, pets, use of gas for cooking, and municipality (BAMSE only).

generalised estimation equations with a logit-link using a five-dependent, three-dependent, two-dependent correlation matrix, respectively, 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, because the same procedures were followed in these cohorts, but analysed the South and North subcohorts of the GINI and LISA studies separately. We did separate analyses with exposure at the birth address and exposure at the address at which a participant lived at the time of the follow-up, accounting for changes in exposure due to changes in address. We analysed associations by undertaking cohort-specific analyses with subsequent random-effects meta-analysis,[21] and by pooling data from the various cohorts.

We obtained information about important covariates such as sex; parental socioeconomic status; native nationality; maternal and paternal asthma or hay fever; older siblings; breastfeeding for at least 3 months; maternal smoking during pregnancy; smoking, mould or dampness, and furry pets in the child's home; use of natural gas for cooking; and attendance at day-care centres. We defined covariates as similarly as possible across cohorts. We did all analyses with and without adjustment for the covariates; pooled analyses were additionally adjusted for cohort. Time-varying confounders were selected from the questionnaire that coincided best with the exposure period. We assessed heterogeneity between cohort-specific effect estimates with the I^2 statistic.[22]

We did a sensitivity analysis to establish to what extent the results for PIAMA were affected by use of data from specific follow-up visits (ages 1, 2, 4, 8, 11, and 14 years) rather than data from all visits (ie, yearly follow-ups until age 8, 11, and 14 years). We obtained age-specific and sex-specific effect estimates from pooled analyses with exposure–age and exposure–sex interaction terms. We entered levels of air pollution as continuous variables without transformation in all models. Associations are presented for fixed exposure increments. We did analyses with SAS (version 9.2), except for meta-analyses, which we did with Stata (version 10.1).

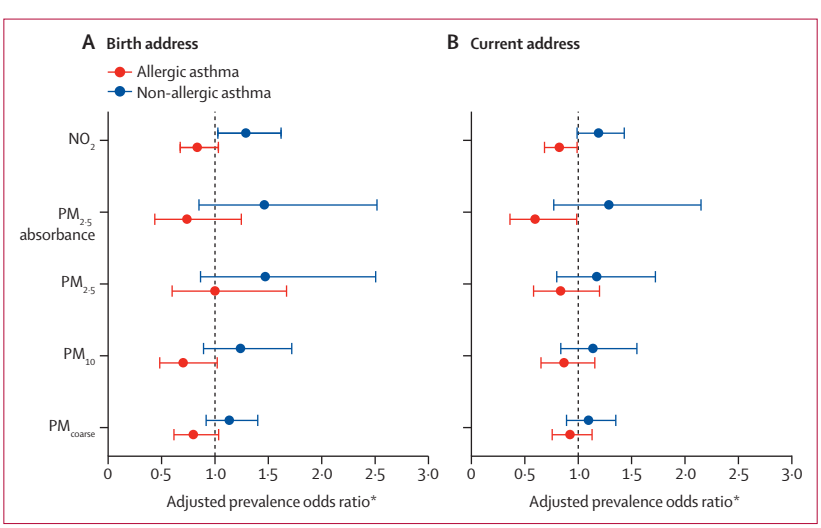

***Figure 4*: Adjusted odds ratios of the associations of air pollution exposure at the birth and current addresses with prevalence of allergic and non-allergic asthma from pooled analysis**

Error bars show 95% CIs. NO_2=nitrogen dioxide. $PM_{2·5}$=particulate matter with a diameter of less than 2·5 μm. PM_{10}=less than 10 μm. PM_{coarse}=particulate matter with a diameter between 2·5 μm and 10 μm. *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 or dampness at home, pets, use of gas for cooking, municipality (BAMSE only), and cohort.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our study sample included 98% of the original participants from the BAMSE (4010/4089 [98%]) and PIAMA (3867/3962 [98%]) cohorts and roughly 80% of the original participants from the GINI and LISA North (2691/3390 [79%]) and South (3558/4416 [81%]) cohorts. The table shows characteristics of the study population and figure 1 shows frequency distributions of health outcomes. More than a third of the participants from the BAMSE and PIAMA cohorts, and 10–15% of those from the GINI and LISA cohorts, developed asthma during follow-up, and roughly a quarter to a third of all participants developed rhinoconjunctivitis (figure 1).

Appendix p 9 presents data for distributions of exposures at participants' home addresses at birth and at 14–16 years. Although more than half of participants changed address at least once during follow-up (table), correlations between exposures at the birth address and at the follow-up addresses were moderate to high (appendix pp 12, 13). Correlations were highest for the PIAMA cohort (r 0·61–0·81 for the 14 year addresses) and lowest for the BAMSE cohort (r 0·34–0·44 for the 16 year addresses; appendix pp 12, 13).

Overall, after adjustment for potential confounders, the risk of incident asthma up to age 14–16 years increased with increasing exposure to NO_2 (adjusted meta-analysis odds ratio 1·13 per 10 μg/m³ [95% CI 1·02–1·25]) and $PM_{2·5}$ absorbance (1·29 per 1 unit [1·00–1·66]) at the birth address, but not with exposure at the address at the time of follow-up (figure 2). We recorded similar, albeit non-significant, associations between air pollution exposure and asthma prevalence (figure 3). There was no indication of an adverse effect of air pollution exposure on rhinoconjunctivitis incidence and prevalence (appendix pp 14, 15). Changes in associations due to confounder adjustment were generally small (appendix pp 16, 17). Heterogeneity of cohort-specific effect estimates was low to moderate for asthma and generally moderate to large for rhinoconjunctivitis (appendix p 10). Effect estimates

from pooled analyses were generally not different from effect estimates from meta-analyses (appendix pp 18, 19).

When we distinguished between allergic and non-allergic asthma (*vs* no asthma), associations with NO_2 exposure seemed to be limited to non-allergic asthma (figure 4). Associations with air pollution for allergic rhinoconjunctivitis (appendix p 20) were similar to associations for rhinoconjunctivitis overall.

In analyses with exposure–age interaction terms, exposure to NO_2, $PM_{2.5}$ absorbance, and $PM_{2.5}$ at the birth address were consistently associated with increased asthma incidence and prevalence after age 4 years; associations were variable before that age (figure 5, appendix p 21). As with overall associations, age-specific associations between exposures at the current address and asthma were less often statistically significant than associations with exposures at the birth address (appendix pp 22, 23). For rhinoconjunctivitis, we recorded little variation in associations with air pollution exposure and age (appendix pp 24, 25).

Although the positive overall associations between air pollution and asthma prevalence and incidence were largely determined by the PIAMA cohort (appendix p 11), positive associations with air pollution after age 4 years were also shown in the other cohorts (appendix pp 26, 27). Associations of air pollution exposure with health outcomes in PIAMA were relatively unchanged when we included information from all follow-up visits until age 14 years instead of information from the common follow-up ages with the other cohorts only (appendix pp 28, 29). Associations between air pollution and asthma tended to be stronger in boys than in girls, but differences were neither statistically significant nor clinically relevant; no clear trend was shown for rhinoconjunctivitis (appendix pp 30, 31).

Discussion

Our findings provide 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 rhino-conjunctivitis, throughout childhood and adolescence. The adverse effects of air pollution on asthma incidence and prevalence were more consistent after age 4 years than before that age.

The present study, using data from four large prospective birth cohort studies with 14–16 years of follow-up, is a major extension of previous collaborative work investigating air pollution and asthma within the same cohorts:[9] we did longitudinal rather than cross-sectional analyses, making full use of the repeated

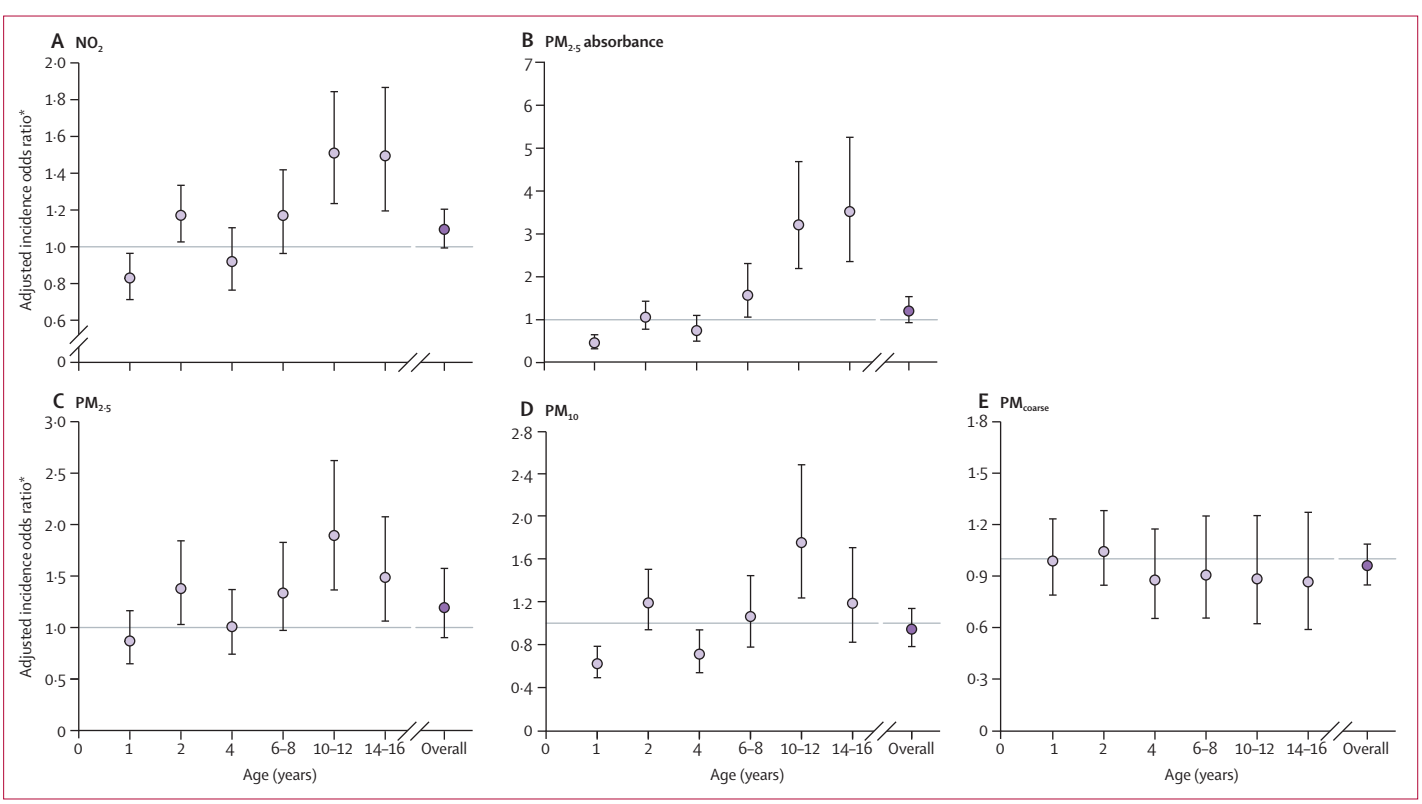

Figure 5: **Adjusted age-specific odds ratios of the association of air pollution exposure at the birth address with asthma incidence from pooled analyses**
Error bars show 95% CIs. NO_2=nitrogen dioxide. $PM_{2.5}$=particulate matter with a diameter of less than 2·5 μm. PM_{10}=less than 10 μm. PM_{coarse}=particulate matter with a diameter between 2·5 μm and 10 μm. *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 or dampness at home, pets, use of gas for cooking, municipality (BAMSE only), and cohort.

measurements; we studied associations with both incidence and prevalence; follow-up was extended to age 14–16 years; and we did pooled and cohort-specific analyses with subsequent meta-analyses, resulting in more precise estimates of age-specific effects. Our finding of an increase in asthma incidence with increasing levels of air pollution confirms previous findings from other cohorts.[6,23–25] The somewhat stronger associations with early life exposure compared with more recent exposure, and the more consistent associations with asthma incidence after age 4 years, confirm findings from the Swedish and Dutch cohorts.[3,5] A similar pattern of inverse associations of NO_2 with onset of asthma before age 4 years, and positive, albeit non-significant, associations thereafter, was reported in a Norwegian cohort of 9–10 year olds.[26] However, significant positive associations between air pollution and asthma development up to age 3–4 years were shown in a Canadian birth cohort.[25] Most other studies did not differentiate pre-school (age <6 years) from school-age (age ≥6 years) onset of asthma.

The more consistent associations after age 4 years might be because young children are difficult to diagnose with asthma,[27] making outcome misclassification more of a concern during the first 4 years of life than thereafter. Misclassification is probably non-differential (ie, not related to air pollution exposure), thus biasing effects towards the null. Diagnostic conventions for asthma are different in the countries of the four cohorts. Because only a few children with reports of symptoms in early childhood develop 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 diagnostic variability might explain differences between cohorts in asthma frequencies before age 4 years. Asthma incidence reported in participants from other cohorts within the same age range[24–26] were between the incidence in the German cohorts and that 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, which triggers inflammation, is thought to be the main mechanism underlying the association between ambient air pollution and asthma.[1] Only a few studies[3,5,29] so far have distinguished allergic from non-allergic asthma. The stronger associations with non-allergic asthma compared with allergic asthma in the present study confirm findings for the Swedish and Dutch cohorts.[3,5] A cohort study from California[29] investigated effects of air pollution in strata of children with and without a history of allergic symptoms and showed stronger effects in children with no allergic symptoms. One suggestion is that the effects of air pollution exposure on non-allergic asthma might be explained by increased non-allergic inflammation.[30] The inconsistency of the cohort-specific effect estimates, in addition to the overall absence of an association between air pollution and rhinoconjunctivitis, is in line with the absence of association between air pollution and allergic sensitisation at ages 4 and 8 years in a 2014 meta-analysis,[31] and supports the conclusions of a 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 issue is a limitation of population studies investigating long-term air pollution effects under real-life conditions. However, there is also merit in quantification of joint effects of air pollution mixtures.[32] NO_2 has previously been suggested to merely act as a surrogate for a complex mix of air pollution; however, WHO investigators concluded that NO_2 individually or in combination with other pollutants is likely to cause adverse health effects.[33] No consistent associations were identified with particle mass ($PM_{2.5}$, PM_{10}, and PM_{coarse}), possibly because of the generally worse performance of land-use regression models for particle mass than for NO_2 and $PM_{2.5}$ absorbance.

Strengths of our study are the large sample size, the length of follow-up, the standardised exposure assessment together with the harmonisation of outcome and confounder data between cohorts, and the pooling of cohort-specific datasets. A limitation of our study might be that we used exposure models based on air pollution measurement campaigns from 2008–10 to assess exposure to air pollution for the entire duration of follow-up. Although the measurement campaigns coincided with the most recent follow-ups of the cohorts, this restriction could be problematic for assessment of historical exposures. Our assumption of the spatial contrasts in levels of air pollution 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 7 years and more.[34–36] By using purely spatial land-use regression 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 the other study areas, NO_2 and $PM_{2.5}$ concentrations decreased by about 30% from 1999 to 2009.[37,38] This decrease might have biased associations with more recent exposure, but is not an issue for analyses with early life exposures that solely rely on spatial contrasts within cohorts. That we solely relied on residential exposures and did not include either exposure at locations other than home or time–activity pattern is another potential limitation. During pre-school years, this limitation is more of a concern for the Swedish and Dutch cohorts, in which day-care attendance is more common than in German cohorts; however, at school age, the effect is probably 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 reliance on

residential exposure only is likely non-differential. Spatial clustering and confounding of associations by area-level socioeconomic status have been explored in the framework of previous analyses within the same cohorts and have not been identified.[10,31] In our study sample, children of atopic parents and those of highly educated parents were over-represented. Because the results were largely unchanged by adjustment for potential confounders, including parental atopy and parental education, this over-representation most likely did not affect our results.

In conclusion, exposure to air pollution early in life can contribute to the development of asthma throughout childhood and adolescence.

Contributors

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

Declaration of interests

GHK has received grants from TEVA outside of the submitted work. DSP has received funding to his institution for an unrestricted educational grant for research from AstraZeneca and Chiesi; consultancy fees to his institution from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline (GSK), Nycomed, and TEVA; partial funding from AstraZeneca, Chiesi, GSK, and Nycomed for travel to European Respiratory Society and American Thoracic Society meetings; and payment for lectures in China and associated travel expenses from Chiesi. JB has received personal fees outside of the submitted work from Actelion, Almirall, Meda, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, TEVA, and Uriach for advisory board membership; Almirall, AstraZeneca, Chiesi, GSK, Meda, Merck, MSD, Novartis, OM Pharma, Sanofi-Aventis, Schering Plough, Takeda, TEVA, and Uriach for lectures during meetings; and Stallergènes for board of directors membership. All other authors declare no competing interests.

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