EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Gehring U, Wijga AH, Koppelman GH, *et al*. Air pollution and the development of asthma from birth until young adulthood. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00147-2020).

Air pollution and the development of asthma from birth until young adulthood

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Take home message

Exposure to air pollution, especially from motorized traffic, early in life may have long-term consequences for asthma development as it is associated with an increased odds of developing asthma through childhood and adolescence into early adulthood.

Word count abstract: 246 words

Word count introduction-conclusions: 3,317 words

Abstract

Background: Air pollution is associated with asthma development in children and adults, but the impact on asthma development during the transition from adolescence to adulthood is unclear. Adult studies lack historical exposures and consequently cannot assess the relevance of exposure during different periods of life. We assessed the relevance of early life and more recent air pollution exposure for asthma development from birth until early adulthood.

Methods: We used data of 3,687 participants of the prospective Dutch PIAMA birth cohort and linked asthma incidence until age 20 to estimated concentrations of nitrogen dioxide (NO_2), $PM_{2.5}$ absorbance ("soot") and particulate matter with a diameter <2.5 μm ($PM_{2.5}$), <10 μm (PM_{10}), and 2.5-10 μm (PM_{coarse}) at the residential address. We assessed overall and age-specific associations with air pollution exposure with discrete time hazard models, adjusting for potential confounders.

Results: Overall, we found higher incidence of asthma until age 20 with higher exposure to all pollutants at the birth address [adjusted odds ratio (95% confidence interval) ranging from 1.09 (1.01-1.18) for PM_{10} to 1.20 (1.10-1.32) for NO_2) per interquartile range increase] that were rather persistent with age. Similar associations were observed with more recent exposure defined as exposure at the current home address. In two-pollutant models with PM, associations with NO_2 persisted.

Conclusions: Exposure to air pollution, especially from motorized traffic, early in life may have long-term consequences for asthma development as it is associated with an increased odds of developing asthma through childhood and adolescence into early adulthood.

Key words: air pollution, asthma, birth cohort, childhood, adulthood

Introduction

Asthma is one of the major non-communicable diseases and has been estimated to affect 339 million people worldwide [1]. It is a heterogeneous disease, usually characterized by chronic airway inflammation and defined by a history of respiratory symptoms that vary over time and in intensity, together with variable expiratory airflow limitation [2]. Asthma can develop at any age, but most asthmatics develop the first symptoms in childhood [2]. Both genetic and environmental factors contribute to the disease [1].

There is growing evidence from prospective cohort studies that exposure to ambient air pollution increases the risk of developing asthma in children, e.g. [3, 4] and some evidence for such a relationship in adults [5-12]. The impact of air pollution on asthma development during the transition from adolescence to adulthood, however, is currently unclear. Some of the studies in children [13, 14] and most of the studies in adults include some adolescents and/or young adults, but participants aged 17 to 20 years are generally underrepresented and air pollution effect estimates are not presented for that specific age group. Another limitation of the studies in adults is the lack of historical exposures before enrolment into the study, making it impossible to study the relevance of exposure at different time points.

Several mechanisms have been proposed for how air pollution contributes to asthma development including oxidative stress and damage, airway remodeling, inflammatory pathways and immunological responses, and enhancement of respiratory sensitization to aeroallergens [16].

This study extends previous analyses until age 14 within the prospective PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study [17]. We added data collected at ages 17 and 20 years and assessed the long-term overall and age-specific effects of

outdoor air pollution exposure early in life and more recently on incident asthma from birth until age 20.

Materials and Methods

Study design and study population

Details on the PIAMA birth cohort study have been published elsewhere [18, 19]. In brief, pregnant women were recruited from the general population through antenatal clinics in the north, west and center of the Netherlands in 1996-1997. The study started with 3,963 newborns. Parents completed questionnaires on demographic factors, risk factors for asthma and respiratory symptoms at birth, at the child's ages of 3 months and 1 year and then annually until the age of 8 years. At ages 11, 14, and 17 years, both the parents and the participants themselves completed questionnaires, and at age 20 only the participants completed questionnaires. For the present analysis, all participants with data on incident asthma and data on air pollution exposure at the birth address and/or current address for at least one of the questionnaire surveys were included (N=3,687), of which 90% (3,314/3,687) had data for 7 or more of the 12 questionnaire surveys and only few (59/3,687=3%) had data for a single questionnaire survey only.

The Institutional Review Boards of the participating institutes approved the study protocol, and written informed consent was obtained from the parents or legal guardians of all participants

Definition of asthma

Information on the participant's respiratory health was collected by repeated questionnaires from birth until age 20. 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? (Has a doctor ever told you that you have asthma?)", 2) "Has your child (have you) had wheezing or whistling in the chest in the last 12 months?", 3) "Has your child (have you) been prescribed asthma medication during the last 12 months?", a definition that has been developed by a panel of experts within the MeDALL consortium [20]. Incident asthma was defined positive the first time a participant fulfilled the criteria for asthma described above if participants had non-missing data for all previous follow-ups. Incident asthma was defined negative if a participant did not fulfill the criteria in the respective year and all previous years. Data for participants with missing information on asthma for one or more follow-ups were right censored and incident asthma was defined missing from the first follow-up with missing data onwards.

Air pollution exposure assessment

Annual average air pollution concentrations at the participants' birth address and current home addresses at the different follow-ups were estimated by Land-Use Regression (LUR) models described elsewhere [21, 22] and in the Supplementary Material. In brief, three two-week air pollution monitoring campaigns were performed in 2008-2010 and NO_2, "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 measured and results were averaged to estimate the annual average [22]. Predictor variables on nearby traffic, population/household density and land use derived

from Geographic Information Systems were evaluated to explain spatial variation in annual average concentrations as described in the online Supplement. Regression models (Table E1 of the Supplementary Material) were developed and then used to estimate annual average air pollution concentrations at the participants' home addresses.

Covariates

Covariates were selected *a priori* based on literature. Sex, maternal and paternal asthma and/or hay fever (yes/no), Dutch nationality (both parents being born in the Netherlands, yes/no), parental education (maximum educational level attained by the mother or father, low/medium/high, breastfeeding at 12 weeks (yes/no), older siblings (yes/no), and maternal smoking during pregnancy (yes/no) were obtained from questionnaires completed during pregnancy or the child's first year of life; daycare attendance (yes/no) was obtained from the 2-year questionnaire. Smoking in the participant's home, yes/no), mold/damp spots in the living room and/or participant's bedroom (yes/no), and gas cooking (yes/no) has been obtained from the parental questionnaires from birth until age 17 and questionnaires completed by the participants themselves at age 20. Information on active smoking of the participants (at least once a week, yes/no) was obtained from the questionnaires completed by the participants from age 14 onwards.

Statistical analysis

Associations of air pollution exposure with asthma incidence from birth until age 20 were analysed with discrete-time hazard models [23]. In brief, we divided the follow-up until age 20 into 12 discrete periods (i.e. periods in between questionnaires, that is periods of 1 year

until age 8 and periods of 3 years afterwards) and modelled the conditional probability of developing asthma in each discrete time period, given that a participant did not have asthma in any earlier time period in relation to air pollution exposure. Separate analyses were performed with early life exposure (defined as exposure at the birth address) for all time periods and more recent exposure (defined as exposure at the current home address) at a specific follow-up for the respective period, taking into account changes in exposure due to changes in address. Time-varying confounders (mold/damp spots, use of gas cooking, passive and active smoking) were selected from questionnaires that coincided best with the exposure period. Age- and sex-specific effects were obtained by adding exposure-age and exposure-sex interaction terms, respectively, to the models described above. Attrition bias is a concern in cohorts with long follow-ups and was explored as part of a sensitivity analysis among those with nearly complete follow-up (at least 11 out of the 12 questionnaires). We defined more recent exposure for a specific period as exposure at the home address at the time of questionnaire completion (i.e. at the end of that period) and temporality might be a concern for those who changed address between follow-ups. Moreover, we assessed to what extent associations with more recent exposure were sensitive to our definition of more recent exposure by defining more recent exposure as exposure at the home address at the preceding follow-up. Since asthma is difficult to diagnose in very young children, we restricted our analysis to data from age 4 onward as part of a sensitivity analysis to assess to what extent associations were driven the high incidence before the age of four years in our cohort.

Air pollution levels were entered one by (one unless stated otherwise) as continuous variables without transformation in the analyses described above. All associations are presented as odds ratios (OR) with 95% confidence intervals (CI) for an interquartile range

increase in exposure at the birth address. All analyses were performed with the Statistical Analysis System (SAS 9.4, Cary, NC, USA).

Results

Population characteristics

The study sample consists of 93% of the baseline cohort. Differences in characteristics between all participants and those who completed the 20-year questionnaire (2,135/3,678=58%) were small (Table E2). Characteristics of the study population are presented in Table 1. Age-specific prevalence and incidence of asthma are presented in Table 2; age- and sex-specific incidence are presented in Figure E1 of the Supplementary Material.

Air pollution exposure

Distributions of exposures at the birth address and home addresses at the 20-year follow-up were very similar (Table 3). Exposure contrasts were larger for NO_2 and $PM_{2.5}$ absorbance (maximum-minimum ratios 3.5–9.6) than for particle mass concentrations (maximum-minimum ratios 1.4-1.9). Correlations between exposures at the birth address and at home addresses at the different follow-ups were moderate to high until age 17 and much lower at age 20; e.g. correlations ranged from 0.76 to 0.97 for NO_2 and from 0.58 to 0.96 for PM_{10} until age 17 and decreased to 0.55 and 0.38, respectively, for age 20 (Figure E2 of the

Supplementary Material). Correlations between exposures at the same age were highest for NO_2 and $PM_{2.5}$ absorbance (r=0.88-0.91).

Air pollution and asthma incidence

Overall, after adjustment for potential confounders, we found a significantly higher incidence of asthma until age 20 years among participants with higher exposure to all pollutants at the birth address with ORs (95% CI) ranging from 1.09 (1.01-1.18) for PM_{10} to 1.20 (1.10-1.32) for NO_2 per interquartile range increase in exposure (Table 4). Incident asthma was also found to be significantly associated with exposure at the home address at the time of the follow-up for all pollutants except PM_{10}, with ORs similar to those for exposures at the birth address.

Age-specific association estimates from analyses with exposure-age interaction terms had wide confidence intervals because of the relatively low number of cases per year, but indicate that associations tend to be generally positive for all ages, except for age 7 for which association estimates where consistently negative. Association estimates for exposures at the birth address were consistent in size from age 4 onwards (with the exception of age 7) for NO_2 and $PM_{2.5}$ absorbance, but not for $PM_{2.5}$, PM_{10} and PM_{coarse} (Figure 1). Age-specific associations with more recent exposure defined as exposure at the current address at the time of follow-up were less consistent between ages (Figure E3 of the Supplementary Material). None of the exposure-age interactions was statistically significant (p-values from 0.3910-0.7869).

Associations of asthma incidence with air pollution tended to be stronger in girls than in boys (Figure E4 of the Supplementary Material), but exposure-sex interactions were not

statistically significant (p-value was 0.0510 for NO_2 at the birth address and > 0.19 otherwise).

Findings from two-pollutant models (Table E3 of the Supplementary Material) suggest that associations with NO_2 are robust against adjustment for particulate matter mass, i.e. $PM_{2.5}$, PM_{10} and PM_{coarse} and that associations with particulate matter mass diminish or disappear completely after adjustment for NO_2. Two-pollutant models with $PM_{2.5}$ absorbance did not produce valid results (variance inflation factors range from 4.0–5.5) due to the high correlations with all other pollutants.

Results remained largely unchanged, except for larger confidence intervals when restricted to the almost 1,700 participants with nearly complete follow-up (Figures E5 and E6 of the Supplementary Material). Findings were not sensitive to the definition of more recent exposure; associations remained unchanged when we used exposure at the home address at the time of the preceding instead of the same follow-up (Table E4 of the Supplementary Material). Also, association estimates remained stable or were slightly larger when we restricted our analysis to ages 4 and older, but confidence intervals became wider due to the smaller number of cases (Table E5 of the supplementary Material).

Discussion

The present study suggests that exposure to air pollution is associated with the development of asthma through childhood and adolescence into early adulthood.

This study extends previous work within this and other European birth cohort regarding the impact of outdoor air pollution on asthma development in children and adolescents up the age of 14-16 years [17] and closes the gap between findings from these and other children's cohorts and findings from adults cohorts [5-12]. Although statistical power to assess age-specific associations is limited in our cohort, association estimates for NO_2 and $PM_{2.5}$ absorbance at the birth address are rather stable from age of 4 onwards and do not seem to decrease in early adulthood. Larger (consortia of) cohorts are needed to confirm our findings. To our knowledge only few other studies assessed the impact of air pollution on asthma development through childhood and adolescence into young adulthood [13, 14, 24] and none of them looked into age-specific associations. The study of the associations between NO_2 and asthma incidence within the Southern California Children's Health Study (CHS) by Jerrett et al. [13] clearly lacks statistical power for such an analysis with only 30 cases in total among 200 participants followed from age 10-18 years, but within the case-control study by Nishimura et al. [14] performed among Latinos and African Americans from the USA and Puerto Rico, with almost 600 cases aged 15 and older this might have been possible. The same holds for the study by Garcia et al. [24] that showed a decline in asthma incidence with reductions in air pollution levels from 1993-2014 among more than 4,000 participants of the CHS aged 10-18 years. The overall association estimates obtained from the present study are somewhat stronger than those reported for children and adolescents up to age 18 by Jerrett et al. [13], Nishimura et al. [14] and a recent review [3], which

correspond to risk ratios (95% confidence interval) of 1.09 (1.02-1.16) , 1.07 (1.02-1.12), and 1.05 (1.02-1.07), respectively for a 9.2 $\mu g/m^3$ increase in NO_2 levels. The less consistent associations between incident asthma and air pollution levels at the birth address until age 4 may be explained by the fact that asthma is difficult to diagnose in very young children [25]. Outcome misclassification, which may also explain in part the higher incidence for that age group as compared to the older ages, is thus a concern. Since neither the participants nor their physicians were aware of the exact air pollution exposure levels, outcome misclassification is likely non-differential and bias in association estimates (if any) would be towards the null. As in previous analyses [17] differences in associations between boys and girls were not statistically significant. Associations with NO_2 and $PM_{2.5}$ absorbance, which are more traffic-related than particulate matter mass concentrations, confirm the role of motorized traffic in these associations that has been suggested by findings of earlier studies showing associations between living near major roads and asthma incidence in children [26] and adults [9]. Due to their high correlation owing to the fact that motorized traffic is a major source of both, NO_2 and $PM_{2.5}$ absorbance, it is impossible to disentangle the contributions of these two exposures to asthma development. Consequently, it remains unclear whether associations are attributable to NO_2 itself as suggested [27, 28] or whether NO_2 acts as a surrogate for a complex mixture of air pollutants. Associations with NO_2 were independent of particle mass concentrations ($PM_{2.5}$, PM_{10} and PM_{coarse}) in our study, whereas associations with particle mass diminish or disappear after adjustment for NO_2. Two-pollutant models behaved slightly different for early life and more recent exposures. Associations with NO_2 at the birth address, but not associations with NO_2 at the current address, tended to become stronger in two-pollutant models; associations with particle mass concentrations (except PM_{10}) at the current address were halved, whereas associations

with particle mass concentrations at the birth address disappeared completely after adjustment for NO_2. The reasons for this are not clear as correlations between pollutants are high and almost identical for the birth and current addresses.

A major strength of the present study over previous studies in adults is the availability of residential histories and exposure histories since birth. This enables us to look into the relevance of exposure at different time points, i.e. exposure early in life defined as exposure at the birth address versus more recent exposure defined as exposure at the address at each follow-up. These analyses with regard to the relevance of the timing of exposure become increasingly interesting as more and more participants move out of their parental home (40% of the current study sample at the time of the 20-year follow-up) and correlations of more recent exposures with early life exposures, which have been high for most of the follow-up, especially for NO_2 and $PM_{2.5}$ absorbance (e.g. r=0.76–0.98 until age 17 for NO_2), finally dropped to values between 0.38 for PM_{10} and 0.55 for NO_2. Nevertheless, the relevance of early life over recent exposure remains unclear as mutually adjusted models with early life and more recent exposure suggest are not feasible yet as for most of the follow-up so far, correlations with exposure at the birth address are high and the number of incident cases from the 20-year follow-up is too small (n=16) to provide meaningful results. These analyses require a longer-follow up or data from multiple cohorts.

Several studies reported stronger associations for non-atopic asthma than for atopic asthma [17, 29] or associations with non-atopic asthma only [14, 30]. A limitation of the present study is the lack of statistical power to analyse associations with atopic and non-atopic asthma separately as measurements of specific IgE to common inhalant allergens were limited to subsets of the current study population and specific ages (685, 1,655, 1,269 and

738 participants at ages 4, 8, 12 and 16, respectively). With between 41% and 53% of the subjects being sensitized to at least one of the allergens tested, numbers of atopic and non-atopic incident asthma cases (n=7 and 13, respectively, at most per age) were too small to provide any meaningful results, again requiring larger or multiple cohorts are needed. Attrition bias is a concern in studies with long follow-ups. However, population characteristics were not very different at age 20 and associations with air pollution were very similar among those with almost complete follow-up. Generalizability to the Dutch general population may be a concern as children of highly educated parents and children of Dutch parents are over-represented [19]. However, at present there is no evidence for a different susceptibility of these groups to the effects of air pollution. Generalizability beyond the Dutch general population may also be a concern, but findings from a recent meta-analysis [3] found no regional heterogeneity in associations of childhood asthma with air pollution. Another limitation is the use of purely spatial land-use regression models for estimation of the participants' residential exposure. The models were developed using data from air pollution measurement campaigns performed between 2008 and 2010 and applied to the residential histories of our study participants over a period of 20 years starting in 1996/97. This means that we used the models to forecast and back-cast exposures for periods of about 11 years, which may have resulted in exposure misclassification and some bias in exposure-response relationships. However, spatial contrasts have been shown to be stable over periods of seven or more years for NO_2 in seven areas including the Netherlands [31-33] and over even longer periods for black smoke in the United Kingdom [34]. Nevertheless, by using purely spatial land-use regression models, we did not account for long-term trends in air pollution levels and may have underestimated exposure contrasts for

the earlier years and overestimated contrasts for the more recent years as NO_2 and PM_{10} concentrations have decreased in the Netherlands over the last decades [35, 36].

In conclusion, exposure to air pollution, especially from motorized traffic, early in life may have long-term consequences for asthma development as it is associated with an increased odds of developing asthma through childhood and adolescence into early adulthood.

Acknowledgements

The authors would like to thank PIAMA participants and parents who contributed to the study and Marjan Tewis for data management.

Financial support

The research leading to these results has received funding from Dutch Lung Foundation (Project number 4.1.14.001). In addition, the PIAMA study was 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. Ulrike Gehring was supported by a Grant of The Netherlands Organization for Scientific Research.

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Figure legends

Figure 1. Adjusted * age-specific associations of air pollution exposure early in life (i.e. at the birth address) with asthma incidence until age 20 (N=3,141 subjects).

* adjusted for sex, maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

Table 1. Participant characteristics (N=3,687).

Variable	n/N	(%)
Female sex	1,780/3,687	(48.3)
Maternal asthma and/or hay fever	881/3,652	(24.1)
Paternal asthma and/or hay fever	911/3,658	(24.9)
Dutch nationality	3,190/3,521	(90.6)
High maternal education	1,298/3,678	(35.3)
High paternal education	1,458/3,637	(40.1)
Breastfeeding (≥12 weeks)	1,627/3,463	(47.0)
Older siblings	1,860/3,678	(50.6)
Day-care center attendance *	2,040/3,538	(57.7)
Mother smoked during pregnancy	626/3,652	(17.1)
Smoking at child's home †		
Early life ‡	912/3,686	(24.7)
Age 20	186/2,127	(8.7)
Active smoking ≥ 1x/week §		
Age 14	119/2,431	(4.9)
Age 20	426/2,127	(20.0)
Use of natural gas for cooking		
Early life ‡	3,028/3,674	(82.4)
Age 20	1,564/2,127	(73.5)
Mold/damp spots in participant's home		
Early life ‡	300/3,643	(8.2)
Age 20	242/2,127	(11.4)
Furry pets in participant's home		
Early life ‡	1,720/3,677	(46.8)
Age 20	877/2,127	(41.2)
Change of address between birth and most recent follow-up	2,637/3,687	(71.5)

* during 2nd year of life

† defined as parental smoking until and including age 17 and any smoking at age 20

‡ during first year of life

§ at age 14 and older

Table 2. Age-specific prevalence and incidence of asthma.

Age	Prevalence		Incidence	
(years)	n/N	(%)	$n/N_{at\ risk}$	(%)
1	221/3,687	(6.0)	221/3,687	(6.0)
2	213/3,551	(6.0)	80/3,346	(2.4)
3	353/3,503	(10.1)	201/3,172	(6.3)
4	291/3,393	(8.6)	79/2,838	(2.8)
5	279/3,360	(8.3)	56/2,652	(2.1)
6	273/3,336	(8.2)	39/2,525	(1.5)
7	219/3,247	(6.7)	34/2,411	(1.4)
8	230/3,194	(7.2)	25/2,285	(1.1)
11	174/2,570	(6.8)	23/1,824	(1.3)
14	157/2,271	(6.9)	28/1,491	(1.9)
17	93/1,827	(5.1)	11/1,188	(0.9)
20	157/2,135	(7.4)	16/1,031	(1.6)

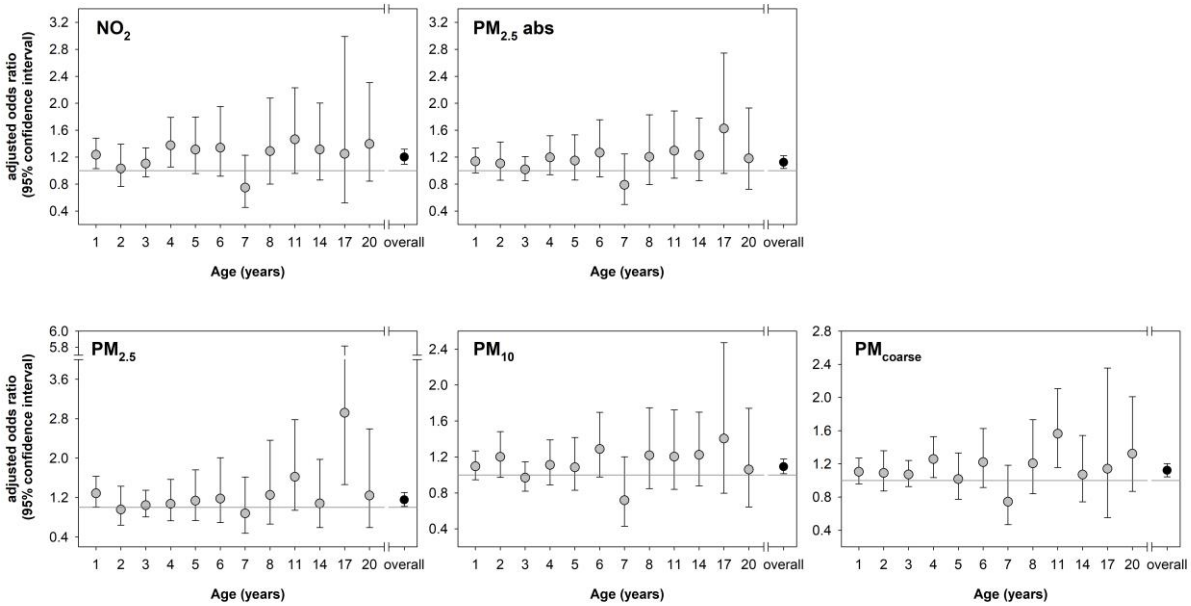
Table 3. Distribution of estimated annual average air pollution levels at the participants' birth addresses and home addresses at the most recent (20-year) follow-up.

	Birth address (N = 3,674)					20-year follow up address (N=2,009)				
Pollutant	**Mean (Std)**	**Min**	**P50**	**Max**	**IQR**	**Mean (Std)**	**Min**	**P50**	**Max**	**IQR**
NO_2 [μg/m³]	24.3 (7.2)	9.1	24.2	87.6	9.2	25.4 (7.3)	9.4	25.0	63.5	8.9
$PM_{2.5}$ abs [$10^{-5}m^{-1}$]	1.26 (0.27)	0.85	1.25	3.11	0.31	1.31 (0.29)	0.85	1.27	2.95	0.31
$PM_{2.5}$ [μg/m³]	16.4 (0.7)	15.3	16.5	21.1	1.2	16.5 (0.8)	14.9	16.5	21.1	1.0
PM_{10} [μg/m³]	25.0 (1.2)	23.7	24.7	33.2	1.2	25.2 (1.3)	23.7	24.9	32.5	1.5
PM_{coarse} [μg/m³]	8.5 (0.9)	7.6	8.2	14.1	0.9	8.5 (0.9)	7.6	8.3	14.1	1.0

Table 4. Crude and adjusted overall associations of air pollution exposure early in life (i.e. at the birth address) and more recently (i.e. at the current address at the time of follow-up) with asthma incidence until age 20.

	Crude			Adjusted *		
Pollutant [increment]	**OR**	**(95% CI)**	**p-value**	**OR**	**(95% CI)**	**p-value**
Birth address	**N=3,674 subjects**			**N=3,141 subjects**		
NO_2 [9.2 μg/m³]	1.19	(1.09-1.29)	0.0001	1.20	(1.10-1.32)	0.0001
$PM_{2.5}$ abs [0.3 $10^{-5}m^{-1}$]	1.11	(1.03-1.20)	0.0046	1.12	(1.03-1.22)	0.0056
$PM_{2.5}$ [1.2 μg/m³]	1.16	(1.04-1.30)	0.0084	1.15	(1.02-1.30)	0.0222
PM_{10} [1.2 μg/m³]	1.07	(1.00-1.15)	0.0387	1.09	(1.01-1.18)	0.0221
PM_{coarse} [0.9 μg/m³]	1.09	(1.02-1.16)	0.0067	1.12	(1.04-1.20)	0.0015
Current address	**N=3,686 subjects**			**N=3,191 subjects**		
NO_2 [9.2 μg/m³]	1.12	(1.03-1.24)	0.0081	1.15	(1.04-1.27)	0.0080
$PM_{2.5}$ abs [0.3 $10^{-5}m^{-1}$]	1.09	(1.01-1.18)	0.0358	1.12	(1.03-1.23)	0.0124
$PM_{2.5}$ [1.2 μg/m³]	1.15	(1.02-1.29)	0.0220	1.19	(1.04-1.36)	0.0094
PM_{10} [1.2 μg/m³]	1.05	(0.97-1.13)	0.2445	1.07	(0.99-1.17)	0.0862
PM_{coarse} [0.9 μg/m³]	1.07	(1.00-1.15)	0.0498	1.11	(1.02-1.20)	0.0114

* adjusted for sex, age, maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking


NO2
PM2.5 abs
PM2.5
PM10
PMcoarse
adjusted odds ratio (95% confidence interval)
Age (years)
1 2 3 4 5 6 7 8 11 14 17 20 overall

Air pollution and the development of asthma from birth until young adulthood

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Online Data Supplement

Materials and Methods

Land-use regression model development

In brief, air pollution monitoring campaigns were performed between October 2008 and February 2010. 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 [1]. 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 (see Table E1 in the online data supplement) were developed as described in the Supplemental Material and then used to estimate annual average air pollution concentrations at the participants' home addresses, for which the same GIS predictor variables were collected.

Linear regression models were developed to maximize the adjusted explained variance, using a supervised stepwise selection procedure, first evaluating univariate regressions of the corrected annual average concentrations with all available potential predictors following procedures used before.[1, 2] The predictor giving the highest adjusted explained variance (adjusted R^2) was selected for inclusion in the model if the direction of effect was as defined a priori. We then evaluated which of the remaining predictor variables further improved the model adjusted R^2, selected the one giving the highest gain in adjusted R^2, and the right direction of effect. Subsequent variables were not selected if they changed the direction of effect of one of the previously included variables. This process continued until there were no more variables with the right direction of effect, which added at least 0.01 (1%) to the adjusted R^2 of the previous model. Model performance was generally good (leave one out cross-validation R^2=61-89%, Table E1), but lower for PM_{coarse} (38%).

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Table E1. Land-use regression models with model R^2.

Pollutant	Land-use regression model	Model R^2	LOOCV R^2
NO_2	$-7.80 + 1.18\times REGIONALESTIMATE + 2.30\times10^{-5}\times POP\_5000 + 2.46\times10^{-6}\times TRAFLOAD\_50 + 1.06\times10^{-4}\times ROADLENGTH\_1000 + 9.84\times10^{-5}\times HEAVYTRAFLOAD\_25 + 12.19\times DISTINVNEARC1 + 4.47\times10^{-7}\times HEAVYTRAFLOAD\_25\_500$	86%	81%
$PM_{2.5}$ absorbance	$0.07 + 2.95\times10^{-9}\times TRAFLOAD\_500 + 2.93\times10^{-3}\times MAJORROADLENGTH\_50 + 0.85\times REGIONALESTIMATE + 7.90\times10^{-9}\times HLDRES\_5000 + 1.72\times10^{-6}\times HEAVYTRAFLOAD\_50$	92%	89%
$PM_{2.5}$	$9.46 + 0.42\times REGIONALESTIMATE + 0.01\times MAJORROADLENGTH\_50 + 2.28\times10^{-9}\times TRAFMAJORLOAD\_1000$	67%	60%
PM_{10}	$23.71 + 2.16\times10^{-8}\times TRAFMAJORLOAD\_500 + 6.68\times10^{-6}\times POP\_5000 + 0.02\times MAJORROADLENGTH\_50$	68%	61%
PM_{coarse}	$7.59 + 5.02\times10^{-9}\times TRAFLOAD\_1000 + 1.38\times10^{-7}\times PORT\_5000 + 5.38\times10^{-5}\times TRAFNEAR$	51%	38%

LOOCV = Leave one out cross-validation

DISTINVNEARC1: Inverse distance to the nearest road; HLDRES_X: Sum of high density and low density residential land in X m buffer; HEAVYTRAFLOAD_X: Total heavy-duty traffic load of all roads in a buffer (sum of (heavy-duty traffic intensity *length of all segments)); MAJORROADLENGTH_X; Road length of major roads in X m buffer; POP_X: Number of inhabitants in X m buffer; REGIONALESTIMATE: Regional estimate; ROADLENGTH_X: Road length of major roads in X m buffer; TRAFNEAR: Traffic intensity on nearest road; TRAFLOAD_X: Total traffic load of all roads in X m buffer (sum of (traffic intensity * length of all segments)); TRAFMAJORLOAD_X: Total traffic load of major roads in X m buffer (sum of (traffic intensity * length of all segments))

Table E2. Participant characteristics for all participants (N=3,687) and those who completed the 20-year follow-up (n=2,135).

	All participants		20-year follow-up	
Variable	**n/N**	**(%)**	**n/N**	**(%)**
Female sex	1,780/3,687	(48.3)	1,124/2,135	(52.6)
Maternal asthma and/or hay fever	881/3,652	(24.1)	493/2,116	(23.3)
Paternal asthma and/or hay fever	911/3,658	(24.9)	525/2,117	(24.8)
Dutch nationality	3,190/3,521	(90.6)	1,916/2,093	(91.5)
High maternal education	1,298/3,678	(35.3)	864/2,132	(40.5)
High paternal education	1,458/3,637	(40.1)	939/2,116	(44.4)
Breastfeeding (≥12 weeks)	1,627/3,463	(47.0)	1,046/2,014	(51.9)
Older siblings	1,860/3,678	(50.6)	1,092/2,134	(51.2)
Day-care center attendance *	2,040/3,538	(57.7)	1,255/2,104	(59.6)
Mother smoked during pregnancy	626/3,652	(17.1)	301/2,121	(14.2)
Smoking at child's home (early life) †	912/3,686	(24.7)	448/2,135	(21.0)
Use of natural gas for cooking (early life) †	3,028/3,674	(82.4)	1,758/2,133	(82.4)
Mold/damp spots in participant's home (early life) †	300/3,643	(8.2)	169/2,109	(8.0)
Furry pets in participant's home (early life) †	1,720/3,677	(46.8)	971/2,133	(45.5)

* during 2nd year of life

† at baseline or during first year of life if no baseline information available

Table E3. Overall associations* of air pollution exposure early in life (i.e. at the birth address) and more recently (i.e. at the current address) with asthma incidence until age 20 from single- and two-pollutant models.

	Single-pollutant		Two-pollutant model with co-pollutant									
			NO_2		$PM_{2.5}$ abs		$PM_{2.5}$		PM_{10}		PM_{coarse}	
Pollutant [increment]	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Birth address (N=3,141 subjects)												
NO_2 [9.2 µg/m³]	1.20	(1.10-1.32)		---	**1.43**	**(1.15-1.80)**	1.24	(1.09-1.42)	1.32	(1.12-1.54)	1.19	(1.02-1.39)
$PM_{2.5}$ abs [0.3 $10^{-5}m^{-1}$]	1.12	(1.03-1.22)	**0.84**	**(0.69-1.03)**		---	**1.14**	**(0.96-1.35)**	**1.17**	**(0.97-1.42)**	1.04	(0.91-1.18)
$PM_{2.5}$ [1.2 µg/m³]	1.15	(1.02-1.30)	0.94	(0.78-1.13)	**0.97**	**(0.76-1.25)**		---	1.09	(0.92-1.30)	1.04	(0.89-1.22)
PM_{10} [1.2 µg/m³]	1.09	(1.01-1.18)	0.91	(0.80-1.04)	**0.96**	**(0.80-1.14)**	1.05	(0.94-1.17)		---	0.97	(0.86-1.11)
PM_{coarse} [0.9 µg/m³]	1.12	(1.04-1.20)	1.01	(0.90-1.13)	1.09	(0.98-1.23)	1.11	(1.01-1.21)	1.14	(1.02-1.29)		---
Current address (N=3,181 subjects)												
NO_2 [9.2 µg/m³]	1.15	(1.04-1.27)		---	**1.12**	**(0.89-1.41)**	1.09	(0.94-1.25)	1.19	(1.01-1.40)	1.10	(0.93-1.29)
$PM_{2.5}$ abs [0.3 $10^{-5}m^{-1}$]	1.12	(1.03-1.23)	**1.03**	**(0.83-1.26)**		---	**1.05**	**(0.88-1.25)**	**1.24**	**(1.01-1.51)**	1.07	(0.93-1.23)
$PM_{2.5}$ [1.2 µg/m³]	1.19	(1.04-1.36)	1.10	(0.92-1.33)	**1.13**	**(0.87-1.46)**		---	1.19	(1.00-1.42)	1.12	(0.96-1.32)
PM_{10} [1.2 µg/m³]	1.07	(0.99-1.15)	0.96	(0.84-1.10)	**0.91**	**(0.75-1.09)**	1.00	(0.89-1.12)		---	0.97	(0.85-1.11)
PM_{coarse} [0.9 µg/m³]	1.11	(1.02-1.20)	1.05	(0.92-1.19)	1.06	(0.94-1.20)	1.06	(0.96-1.17)	1.13	(1.00-1.28)		---

* adjusted for sex, age, maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

Bold: Variance inflation factors ranging from 4.0 – 5.5 indicating multi-collinearity problems. All other variance inflation factors are < 3.

Table E4. Adjusted* overall associations of more recent air pollution exposure, defined as exposure at the at the home address at the time of the preceding follow-up, with asthma incidence until age 20.

	Adjusted		
Pollutant [increment]	**OR**	**(95% CI)**	**p-value**
Current address	**N=3,181 subjects**		
NO_2 [9.2 μg/m³]	1.15	(1.04-1.27)	0.0082
$PM_{2.5}$ abs [0.3 $10^{-5}m^{-1}$]	1.12	(1.02-1.23)	0.0138
$PM_{2.5}$ [1.2 μg/m³]	1.19	(1.04-1.35)	0.0106
PM_{10} [1.2 μg/m³]	1.07	(0.99-1.17)	0.0919
PM_{coarse} [0.9 μg/m³]	1.11	(1.02-1.20)	0.0126

* adjusted for sex, age, maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

Table E5. Crude and adjusted overall associations of air pollution exposure early in life (i.e. at the birth address) and more recently (i.e. at the current address at the time of follow-up) with asthma incidence from age 4 until age 20.

Pollutant [increment]	OR	(95% CI)	p-value
Birth address		**N=2,526 subjects**	
NO_2 [9.2 μg/m³]	1.24	(1.08-1.43)	0.0028
$PM_{2.5}$ abs [0.3 $10^{-5}m^{-1}$]	1.15	(1.01-1.30)	0.0317
$PM_{2.5}$ [1.2 μg/m³]	1.15	(0.95-1.39)	0.1419
PM_{10} [1.2 μg/m³]	1.09	(0.97-1.22)	0.1295
PM_{coarse} [0.9 μg/m³]	1.13	(1.02-1.26)	0.0240
Current address		**N=3,564 subjects**	
NO_2 [9.2 μg/m³]	1.13	(0.96-1.33)	0.1523
$PM_{2.5}$ abs [0.3 $10^{-5}m^{-1}$]	1.14	(0.98-1.31)	0.0871
$PM_{2.5}$ [1.2 μg/m³]	1.22	(0.99-1.51)	0.0611
PM_{10} [1.2 μg/m³]	1.05	(0.92-1.20)	0.4663
PM_{coarse} [0.9 μg/m³]	1.10	(0.97-1.25)	0.1552

* adjusted for sex, age, maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

Figure E1. Overall and sex-specific incidence of asthma at ages 1 to 20 years.

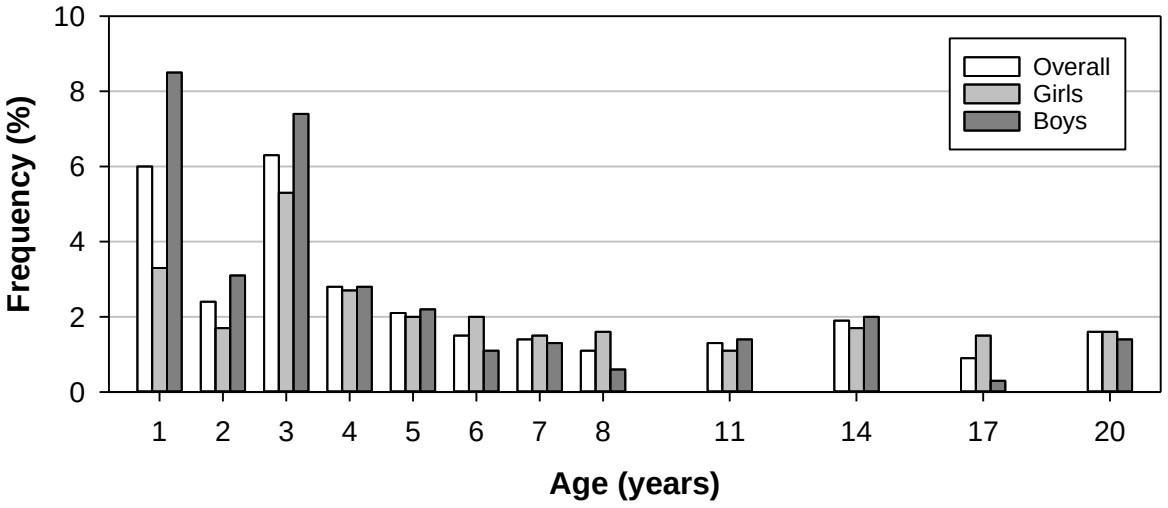


Figure E2. Heatmap of Spearman correlations between air pollutants and follow-ups.

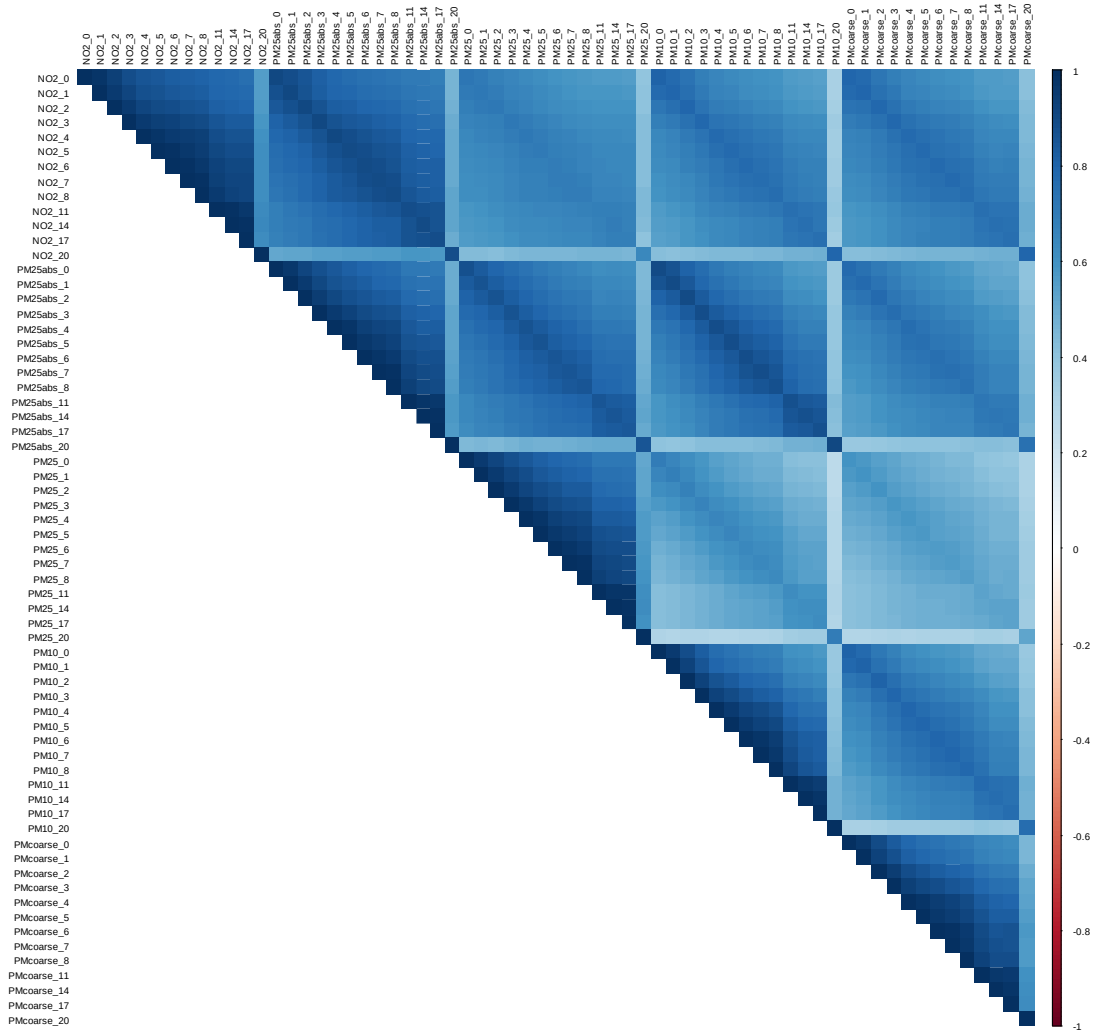
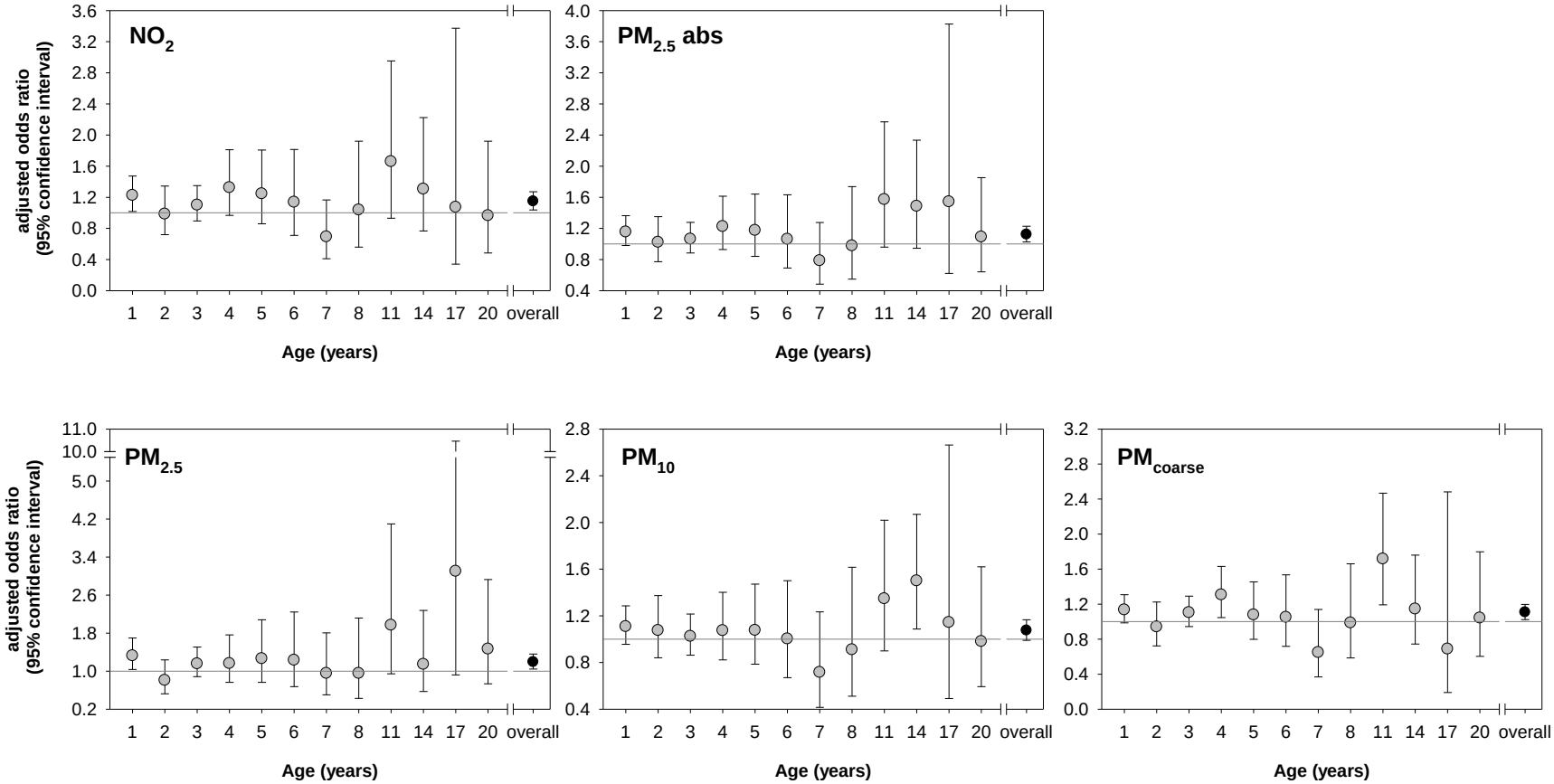
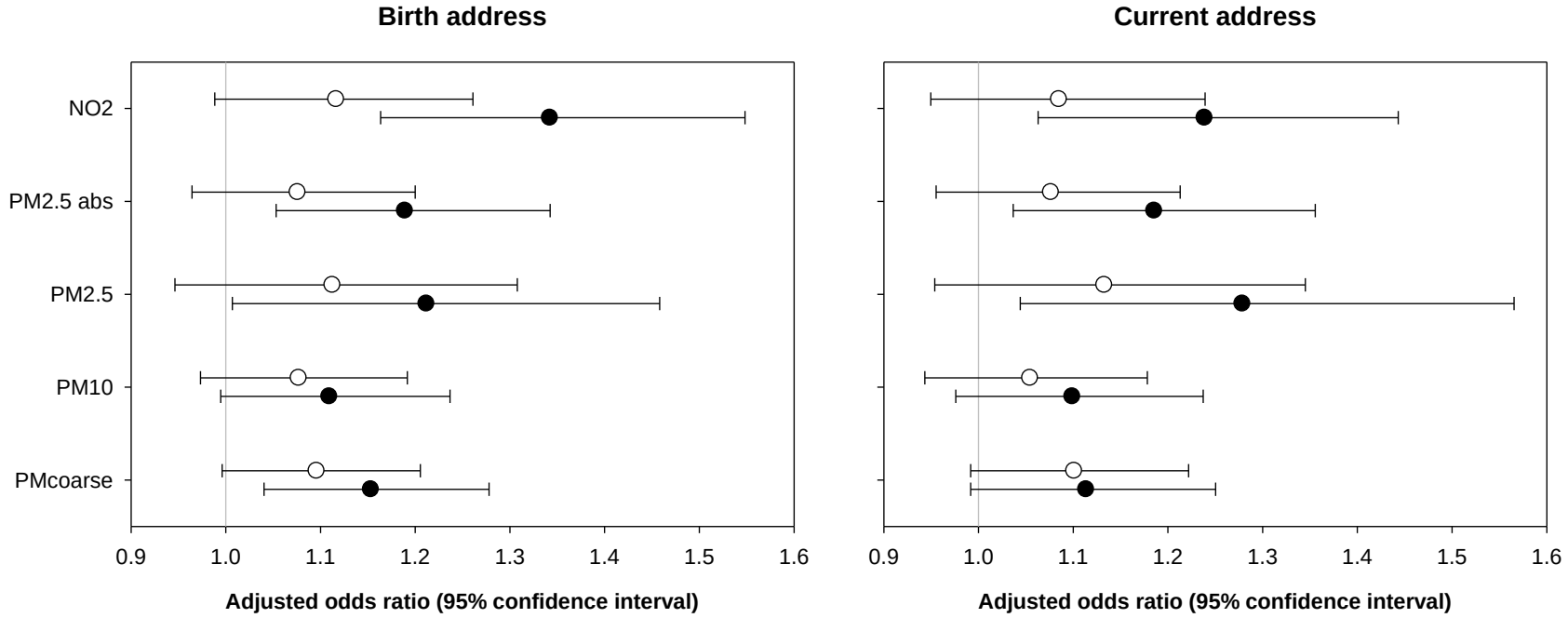


Figure E3. Adjusted * age-specific associations of more recent air pollution exposure (i.e. at the current address at the time of follow-up) with asthma incidence until age 20 (N=3,181 subjects).



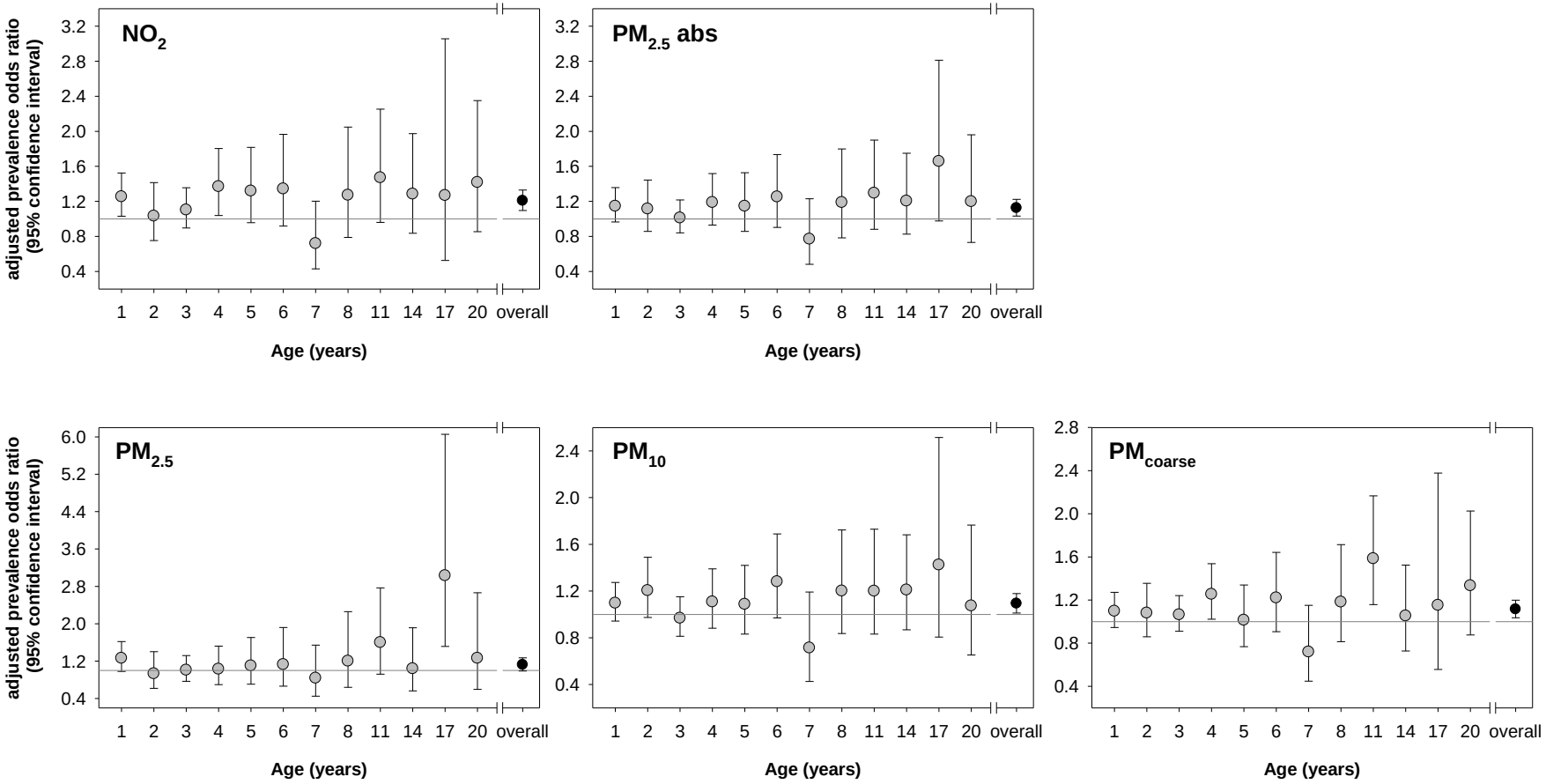
* adjusted for maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

Figure E4. Sex-specific adjusted * associations of air pollution exposure early in life (i.e. at the birth address) and more recently (i.e. at the current address at the time of follow-up) with asthma incidence until age 20 from models with exposure-sex interaction terms. White dots represent boys (N=1,626 participants for birth address, N=1,649 for current address), black dots represent girls (N=1,515 participants for birth address, N=1,532 for current address)**.**



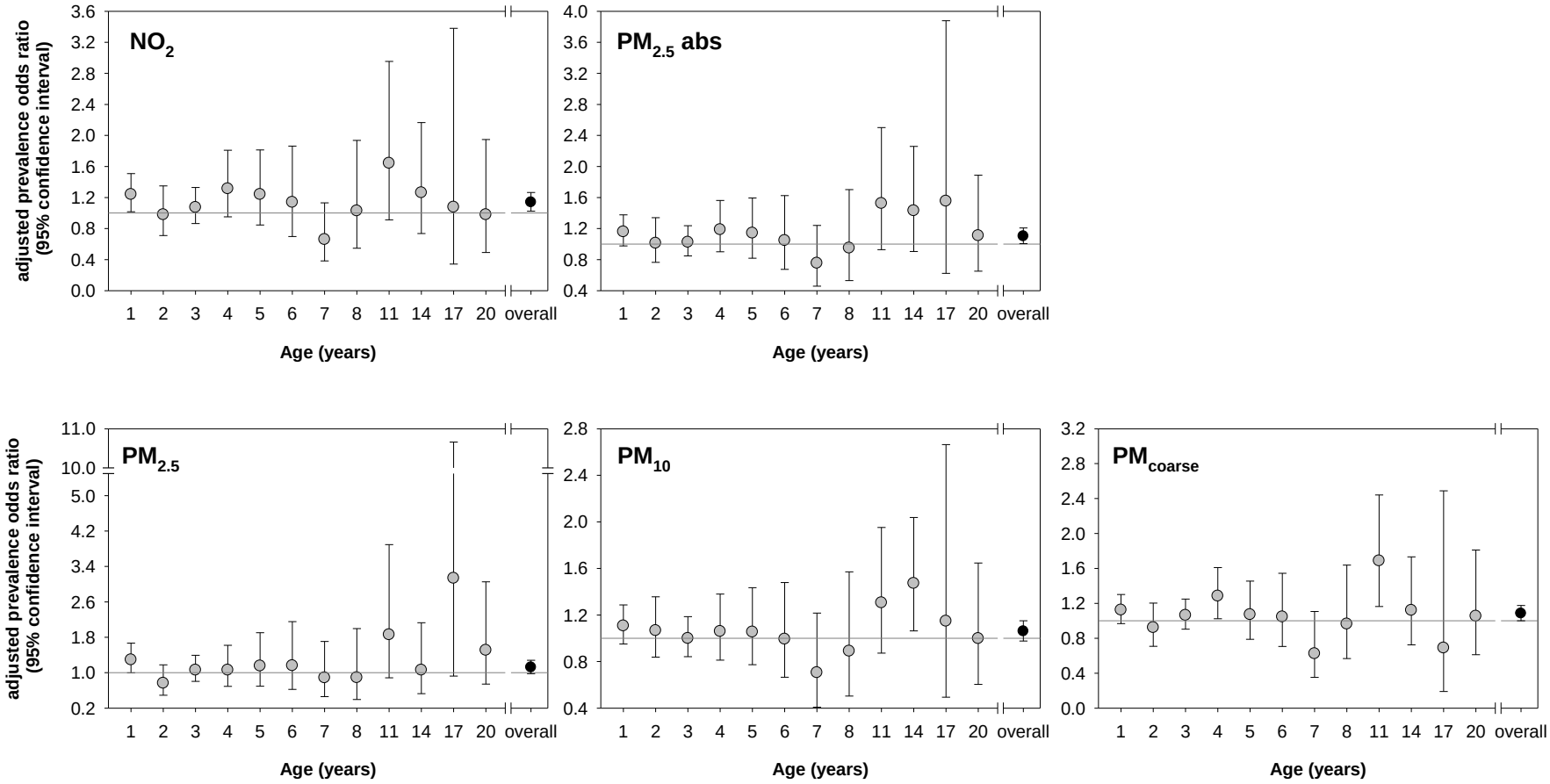
* adjusted for age, maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

Figure E5. Adjusted * age-specific associations of air pollution exposure early in life (i.e. at the birth address) with asthma incidence until age 20 for subjects who participated in at least 11 of the 12 follow-ups (N=1,673 subjects).



* adjusted for maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

Figure E6. Adjusted * age-specific associations of more recent air pollution exposure (i.e. at the current address at the time of follow-up) with asthma incidence until age 20 for subjects who participated in at least 11 of the 12 follow-ups (N=1,698 subjects).



* adjusted for maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking