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

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Early-life exposure to air pollution, especially from motorised traffic, may have long-term consequences for asthma development, as it is associated with an increased risk of developing asthma through childhood and adolescence into early adulthood https://bit.ly/39uZHVH

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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 3687 participants of the prospective Dutch PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort and linked asthma incidence until age 20 years to estimated concentrations of nitrogen dioxide (NO_2), particulate matter with a diameter <2.5 µm ($PM_{2.5}$), <10 µm (PM_{10}), and 2.5–10 µm, and $PM_{2.5}$ absorbance ("soot") 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 the age of 20 years with higher exposure to all pollutants at the birth address (adjusted odds ratio (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) 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 particulate matter, associations with NO_2 persisted.

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

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Introduction

Asthma is one of the major noncommunicable diseases and has been estimated to affect 339 million people worldwide [1]. It is a heterogeneous disease, usually characterised 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 [3, 4], and some evidence for such a relationship in adults [5–12]. However, the impact of air pollution on asthma development during the transition from adolescence to adulthood 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 17–20 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 remodelling, inflammatory pathways and immunological responses, and enhancement of respiratory sensitisation to aeroallergens [15].

This study extends previous analyses up to the age of 14 years within the prospective PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study [16]. 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 the age of 20 years.

Materials and methods

Study design and study population

Details on the PIAMA birth cohort study have been published elsewhere [17, 18]. In brief, pregnant women were recruited from the general population through antenatal clinics in the north, west and centre of the Netherlands in 1996–1997. The study started with 3963 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 years 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=3687), of which 90% (3314 out of 3687) had data for seven or more of the 12 questionnaire surveys, and only few (59 (3%) out of 3687) 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 years. 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? (age 20 years: Has a doctor ever told you that you have asthma?)", 2) "Has your child (age 20 years: Have you) had wheezing or whistling in the chest in the last 12 months?", 3) "Has your child (age 20 years: Have you) been prescribed asthma medication during the last 12 months?"; this definition has been developed by a panel of experts within the Mechanisms of the Development of Allergy (MeDALL) consortium [19]. Incident asthma was defined as positive the first time a participant fulfilled the criteria for asthma if participants had nonmissing data for all previous follow-ups. Incident asthma was defined as negative if a participant did not fulfil 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 models described elsewhere [20, 21] and in the supplementary material. In brief, three 2-week air pollution monitoring campaigns were performed in 2008–2010 and nitrogen dioxide (NO_2), particulate matter with a diameter <2.5 µm ($PM_{2.5}$), <10 µm (PM_{10}) and 2.5–10 µm (PM_{coarse}), and "soot" ($PM_{2.5}$ absorbance, determined as the reflectance of $PM_{2.5}$ filters), were measured and results were averaged to estimate the annual average [21]. 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 supplementary material. Regression models (supplementary table E1) 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), mould/damp spots in the living room and/or participant's bedroom (yes/no) and gas cooking (yes/no) were obtained from the parental questionnaires from birth until age 17 years and questionnaires completed by the participants themselves at age 20 years. Information on active smoking of the participants (at least once a week, yes/no) was obtained from the questionnaires completed by the participants from the age of 14 years onwards.

Statistical analysis

Associations of air pollution exposure with asthma incidence from birth until age 20 years were analysed with discrete-time hazard models [22]. In brief, we divided the follow-up until age 20 years into 12 discrete periods (*i.e.* periods in between questionnaires, that is periods of 1 year until age 8 years 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 (mould/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. 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 ($\geqslant$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. Therefore, 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 years onward as part of a sensitivity analysis to assess to what extent associations were driven the high incidence before the age of 4 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 (95% CI) for an interquartile range increase in exposure at the birth address. All analyses were performed with the Statistical Analysis System (version 9.4; SAS, 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 (2135 (58%) out of 3678) were small (supplementary 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 supplementary figure E1.

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 the age of age 17 years and much lower at 20 years, *e.g.* correlations ranged from 0.76 to 0.97 for NO_2 and from 0.58 to 0.96 for PM_{10} until the age of 17 years and decreased to 0.55 and 0.38,

TABLE 1 Participant characteristics

Female	1780/3687 (48.3)
Maternal asthma and/or hay fever	881/3652 (24.1)
Paternal asthma and/or hay fever	911/3658 (24.9)
Dutch nationality	3190/3521 (90.6)
High maternal education	1298/3678 (35.3)
High paternal education	1458/3637 (40.1)
Breastfeeding (⩾12 weeks)	1627/3463 (47.0)
Older siblings	1860/3678 (50.6)
Daycare centre attendance[#]	2040/3538 (57.7)
Mother smoked during pregnancy	626/3652 (17.1)
Smoking at child's home[¶]	
Early life[+]	912/3686 (24.7)
Age 20 years	186/2127 (8.7)
Active smoking at least once a week[§]	
Age 14 years	119/2431 (4.9)
Age 20 years	426/2127 (20.0)
Use of natural gas for cooking	
Early life[+]	3028/3674 (82.4)
Age 20 years	1564/2127 (73.5)
Mould/damp spots in participant's home	
Early life[+]	300/3643 (8.2)
Age 20 years	242/2127 (11.4)
Furry pets in participant's home	
Early life[+]	1720/3677 (46.8)
Age 20 years	877/2127 (41.2)
Change of address between birth and most recent follow-up	2637/3687 (71.5)

Data are presented as n/N (%). n=3687. [#]: during second year of life; [¶]: defined as parental smoking until and including age 17 years and any smoking at age 20 years; [+]: during first year of life; [§]: at age ⩾14 years.

respectively, at 20 years (supplementary figure E2). 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 the age of 20 years among participants with higher exposure to all pollutants at the birth address with odds ratios (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). In addition, incident asthma was 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 odds ratios similar to those for exposures at the birth address.

TABLE 2 Age-specific prevalence and incidence of asthma

Age years	Prevalence	Incidence
1	221/3687 (6.0)	221/3687 (6.0)
2	213/3551 (6.0)	80/3346 (2.4)
3	353/3503 (10.1)	201/3172 (6.3)
4	291/3393 (8.6)	79/2838 (2.8)
5	279/3360 (8.3)	56/2652 (2.1)
6	273/3336 (8.2)	39/2525 (1.5)
7	219/3247 (6.7)	34/2411 (1.4)
8	230/3194 (7.2)	25/2285 (1.1)
11	174/2570 (6.8)	23/1824 (1.3)
14	157/2271 (6.9)	28/1491 (1.9)
17	93/1827 (5.1)	11/1188 (0.9)
20	157/2135 (7.4)	16/1031 (1.6)

Data are presented as n/N (%).

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					20-year follow-up address				
	Mean±SD	Min	P50	Max	IQR	Mean±SD	Min	P50	Max	IQR
Subjects n			3674					2009		
NO_2 μg·m^{-3}	24.3±7.2	9.1	24.2	87.6	9.2	25.4±7.3	9.4	25.0	63.5	8.9
$PM_{2.5}$ absorbance 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·m^{-3}	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·m^{-3}	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·m^{-3}	8.5±0.9	7.6	8.2	14.1	0.9	8.5±0.9	7.6	8.3	14.1	1.0

IQR: interquartile range; NO_2: nitrogen dioxide; $PM_{2.5}$: particulate matter with a diameter <2.5 μm; PM_{10}: particulate matter with a diameter <10 μm; PM_{coarse}: particulate matter with a diameter 2.5–10 μm.

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 years, for which association estimates where consistently negative. Association estimates for exposures at the birth address were consistent in size from the age of 4 years onwards (with the exception of age 7 years) 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 (supplementary figure E3). None of the exposure–age interactions were statistically significant (p-values from 0.3910 to 0.7869).

Associations of asthma incidence with air pollution tended to be stronger in females than in males (supplementary figure E4), 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 (supplementary table E3) 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

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 the age of 20 years

Pollutant (increment)	Crude		Adjusted[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Birth address				
Subjects n	3674		3141	
NO_2 (9.2 μg·m^{-3})	1.19 (1.09–1.29)	0.0001	1.20 (1.10–1.32)	0.0001
$PM_{2.5}$ absorbance (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·m^{-3})	1.16 (1.04–1.30)	0.0084	1.15 (1.02–1.30)	0.0222
PM_{10} (1.2 μg·m^{-3})	1.07 (1.00–1.15)	0.0387	1.09 (1.01–1.18)	0.0221
PM_{coarse} (0.9 μg·m^{-3})	1.09 (1.02–1.16)	0.0067	1.12 (1.04–1.20)	0.0015
Current address				
Subjects n	3686		3191	
NO_2 (9.2 μg·m^{-3})	1.12 (1.03–1.24)	0.0081	1.15 (1.04–1.27)	0.0080
$PM_{2.5}$ absorbance (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·m^{-3})	1.15 (1.02–1.29)	0.0220	1.19 (1.04–1.36)	0.0094
PM_{10} (1.2 μg·m^{-3})	1.05 (0.97–1.13)	0.2445	1.07 (0.99–1.17)	0.0862
PM_{coarse} (0.9 μg·m^{-3})	1.07 (1.00–1.15)	0.0498	1.11 (1.02–1.20)	0.0114

NO_2: nitrogen dioxide; $PM_{2.5}$: particulate matter with a diameter <2.5 μm; PM_{10}: particulate matter with a diameter <10 μm; PM_{coarse}: particulate matter with a diameter 2.5–10 μm. [#]: 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 years), mould/dampness at home, pets, use of gas for cooking.

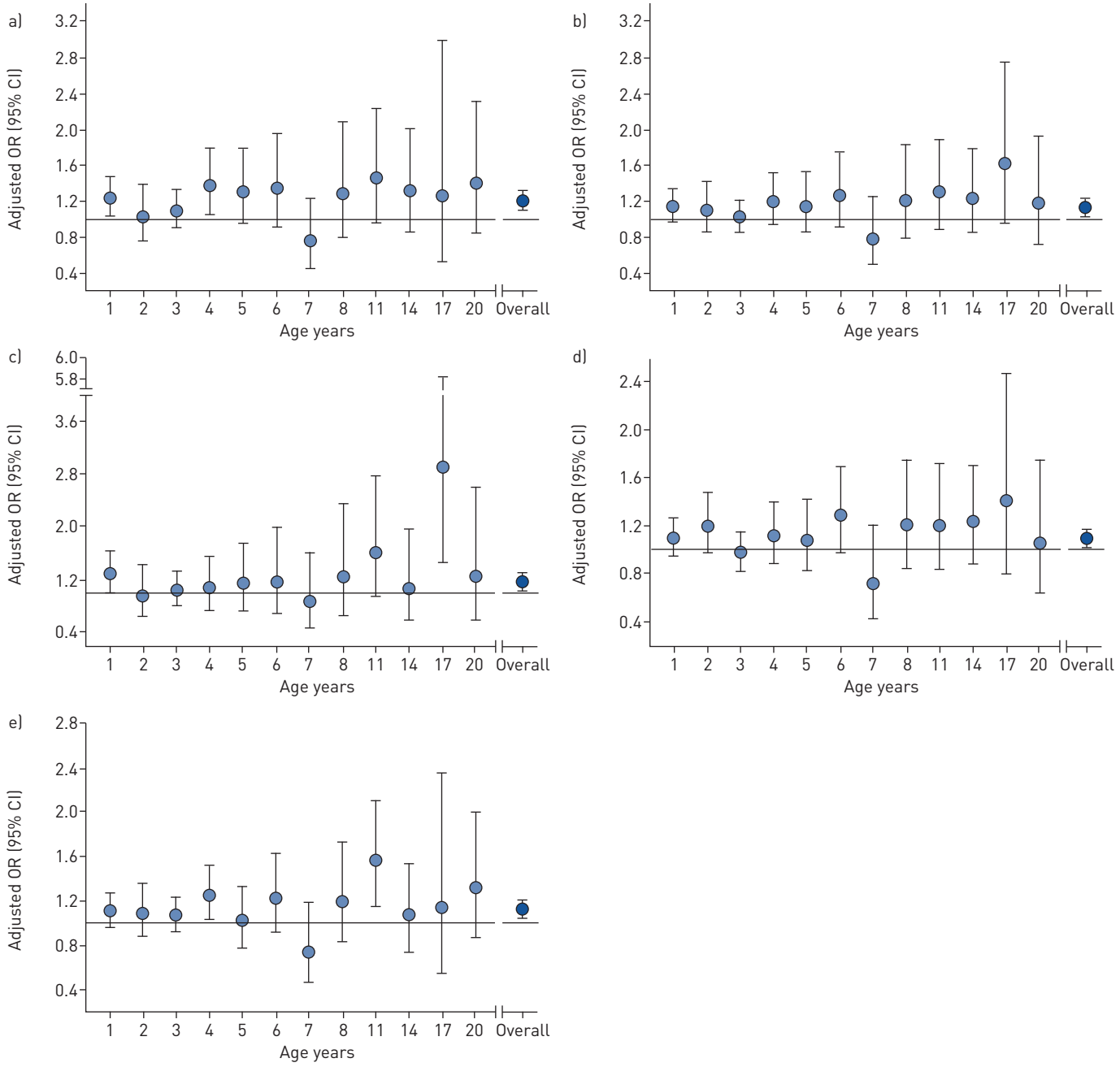

FIGURE 1 Adjusted[#] age-specific associations of air pollution exposure early in life (*i.e.* at the birth address) with asthma incidence until age 20 years (n=3141 subjects). a) nitrogen dioxide; b) particulate matter with a diameter <2.5 µm ($PM_{2.5}$) absorbance; c) $PM_{2.5}$; d) particulate matter with a diameter <10 µm; e) particulate matter with a diameter 2.5–10 µm. [#]: 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 years), mould/dampness at home, pets, use of gas for cooking.

models with $PM_{2.5}$ absorbance did not produce valid results (variance inflation factors range from 4.0 to 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 1700 participants with nearly complete follow-up (supplementary figures E5 and E6). 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 (supplementary table E4). Association estimates remained stable or were slightly larger when we restricted our analysis to ages ⩾4 years, but confidence intervals became wider due to the smaller number of cases (supplementary table E5).

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 cohorts regarding the impact of outdoor air pollution on asthma development in children and adolescents up to the age of 14–16 years [16] and closes the gap between findings from these and other children's cohorts and findings from adult 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 years 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, 23] 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 years, this might have been possible. The same holds for the study by Garcia *et al.* [23] which showed a decline in asthma incidence with reductions in air pollution levels from 1993 to 2014 among >4000 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 years by Jerrett *et al.* [13], Nishimura *et al.* [14] and a recent review [3], which correspond to risk ratios (95% CI) 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 $\mu g \cdot m^{-3}$ increase in NO_2 levels. The less consistent associations between incident asthma and air pollution levels at the birth address until the age of 4 years may be explained by the fact that asthma is difficult to diagnose in very young children [24]. Thus, outcome misclassification, which may also explain in part the higher incidence for that age group as compared to older ages, is a concern. Since neither the participants nor their physicians were aware of the exact air pollution exposure levels, outcome misclassification is probably nondifferential and bias in association estimates (if any) would be towards the null. As in previous analyses [16], differences in associations between males and females 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 motorised traffic in these associations suggested by findings of earlier studies showing associations between living near major roads and asthma incidence in children [25] and adults [9]. Due to their high correlation, owing to the fact that motorised 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 [26, 27], 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 differently 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 years 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: mutually adjusted models with early-life and more recent exposure 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 nonatopic asthma than for atopic asthma [16, 28] or associations with nonatopic asthma only [14, 29]. A limitation of the present study is the lack of statistical

power to analyse associations with atopic and nonatopic asthma separately, as measurements of specific IgE to common inhalant allergens were limited to subsets of the current study population and specific ages (n=685, n=1655, n=1269 and n=738 participants at ages 4, 8, 12 and 16 years, respectively). With between 41% and 53% of the subjects being sensitised to at least one of the allergens tested, numbers of atopic and nonatopic incident asthma cases (n=7 and n=13, respectively, at most per age) were too small to provide any meaningful results, again requiring larger or multiple cohorts. Attrition bias is a concern in studies with long follow-ups. However, population characteristics were not very different at age 20 years and associations with air pollution were very similar among those with almost complete follow-up. Generalisability to the Dutch general population may be a concern, as children of highly educated parents and children of Dutch parents are overrepresented [18]. However, at present there is no evidence for a different susceptibility of these groups to the effects of air pollution. Generalisability 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 1996/1997. 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 $\geqslant$7 years for NO_2 in seven areas including the Netherlands [30–32] and over even longer periods for black smoke in the United Kingdom [33]. 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 recent decades [34, 35].

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

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