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Ambient ultrafine particles and asthma onset until age 20: The PIAMA birth cohort

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ABSTRACT

Rationale: Evidence regarding the role of long-term exposure to ultrafine particles (<0.1 μm, UFP) in asthma onset is scarce.
Objectives: We examined the association between exposure to UFP and asthma development in the Dutch PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort and assessed whether there is an association with UFP, independent of other air pollutants.
Methods: Data from birth up to age 20 years from 3687 participants were included. Annual average exposure to UFP at the residential addresses was estimated with a land-use regression model. Overall and age-specific associations of exposure at the birth address and current address at the time of follow-up with asthma incidence were assessed using discrete-time hazard models adjusting for potential confounders. We investigated both single- and two-pollutant models accounting for co-exposure to other air pollutants ($PM_{2.5}$ and PM_{10} mass concentrations, nitrogen dioxide, and $PM_{2.5}$ absorbance).
Measurements and main results: A total of 812 incident asthma cases were identified. Overall, we found that higher UFP exposure was associated with higher asthma incidence (adjusted odds ratio (95% confidence interval) 1.08 (1.02,1.14) and 1.06 (1.00, 1.12) per interquartile range increase in exposure at the birth address and current address at the time of follow-up, respectively). Age-specific associations were not consistent. The association was no longer significant after adjustment for other traffic-related pollutants (nitrogen dioxide and $PM_{2.5}$ absorbance).
Conclusions: Our findings support the importance of traffic-related air pollutants for asthma development through childhood and adolescence, but provide little support for an independent effect of UFP.

1. Introduction

Asthma is a heterogeneous chronic respiratory disease that affects around 339 million people worldwide (The Global Asthma Report, 2018). In a study from the United Kingdom, up to half of the subjects with asthma experience the first symptoms during childhood (Simpson and Sheikh, 2010). Moreover, the prevalence of asthma in children has been increasing worldwide over the last decade (Ferrante and La Grutta, 2018; Milligan et al., 2016). Both genetic and environmental factors contribute to the etiology of asthma (Papi et al., 2018). Identifying the environmental risk factors is an important step to reduce the disease burden.

Long-term exposure to ambient air pollution has been consistently associated with an increased risk of developing asthma in childhood (Khreis et al., 2017), and there is some evidence for such a relationship in adulthood (Thurston et al., 2020; Liu et al., 2021). Relationships with

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common air pollution metrics including nitrogen dioxide (NO_2), ozone, black carbon and particulate matter with aerodynamic diameters ≤10 μm (PM_{10}) or ≤2.5 μm ($PM_{2.5}$) have been studied intensively and evidence for adverse effects on asthma development from these studies is more consistent for traffic-related air pollutants such as NO_2 and black carbon than for PM mass (Thurston et al., 2020).

Motorized traffic is a major source of ambient ultrafine particles (UFP; defined as particles ≤100 nm in diameter). $PM_{2.5}$ and PM_{10} poorly reflect UFP exposure since UFP do not contribute much to the total particle mass. UFP have been suggested to exert greater toxic effects than larger particles due to their larger surface area/mass ratio, deeper lung penetration, and stronger oxidative capacity (HEI Review Panel on Ultrafine Particles, 2013). A recent meta-analysis of nine epidemiological studies indicated that short-term exposure to ambient UFPs is associated with a significantly higher risk of respiratory hospital admission among children aged 0–14 years (Samoli et al., 2020). However, current epidemiological evidence regarding the impact of long-term exposure to UFP on asthma development is scarce (da Costa e Oliveira et al., 2019; Ohlwein et al., 2019; Wright et al., 2021; Lavigne et al., 2019). Therefore, the World Health Organization (WHO) concluded in their 2021 air quality guideline that more epidemiological evidence regarding the long-term exposure to UFP is needed for the regulation of UFP (WHO Global Air Quality Guidelines, 2021).

We previously reported higher risks of developing asthma from birth until the age of 20 years among subjects with higher exposure to air pollution, especially NO_2 and $PM_{2.5}$ absorbance, within the Dutch PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort (Gehring et al., 2020). The current study extends our previous analyses on air pollution and asthma development by investigating 1) the association of UFP exposure with asthma development using a recently developed national UFP model and 2) whether the association with UFP exposure is independent of other air pollutants.

2. Materials and methods

2.1. Study design and population

PIAMA is a population-based prospective birth cohort study. Detailed descriptions of the PIAMA study have been published previously (Brunekreef et al., 2002; Wijga et al., 2014). In brief, pregnant women were recruited from communities in different regions of the Netherlands in 1996–1997, and their children (N = 3963) were followed up by repeated questionnaire surveys (parental-completed at age 3 months and then annually until age 8, from age 11 onwards every 3 years parent- and -participant completed, and at age 20 participant completed only) including questions about health, demographic factors and risk factors for asthma and respiratory health. Participants with non-missing data on incident asthma and UFP exposure at the birth and/or current address for at least one of the questionnaire-based surveys at ages 1–20 years (n = 3687) were included in the present study.

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.

2.2. Air pollution exposure assessment

Annual average air pollution levels at the participants' residential addresses throughout the follow-up (i.e. from birth until age 20) were estimated using spatial land-use regression (LUR) models that have been described in detail elsewhere (Kerckhoffs et al., 2021; Eeftens et al., 2012; Beelen et al., 2013). In brief, UFP levels were estimated by a national UFP model that we developed recently (Kerckhoffs et al., 2021). The model combines stationary measurements at 20 regional background sites with mobile measurements at 14,392 road segments performed with condensation particle counters (TSI, CPC 3007) from June 2016 to November 2017 as described in more detail previously (Kerckhoffs et al., 2021) and in the online supplement. Land use predictors such as local traffic intensity variables, population density, were presence of ports as well as the regional background concentration were selected by supervised stepwise linear regression into the final model to explain the spatial variation in UFP concentrations. For this analysis, we use the UFP model that was developed using a deconvolution method that segregates UFP concentrations into a local and a background signal which is thought to be more physically realistic.

Long-term exposure to NO_2, $PM_{2.5}$ absorbance ("soot"), and PM mass was assessed using land-use regression models developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE) project as described more extensively in our previous publication (Gehring et al., 2020) and in the online supplement.

Model performance was evaluated using external validation for UFP and internal leave-one out cross-validation for PM mass, $PM_{2.5}$ absorbance and NO_2 and is presented together with the models in Table E1 of the online supplement.

As in previous analyses (Gehring et al., 2020), we defined early life exposure as the annual average exposure at the birth address, and more recent exposure for each of the follow-ups as the annual average exposure at the home address at the time of that specific follow-up. Exposure estimates were derived from the purely spatial LUR models described above without adjustment for temporal trends.

2.3. Asthma ascertainment

We used the same asthma definition as in our previous analysis (Gehring et al., 2020). The definition has been developed within the Mechanisms of the Development of Allergy (MeDALL) consortium (Pinart et al., 2014) and defines asthma as the presence of at least two of the following three conditions: 1) doctor-diagnosed asthma ever, 2) wheezing or whistling in the chest in the last 12 months, and 3) a prescription of asthma medication during the last 12 months. Incident asthma was defined negative if a participant did not fulfill the criteria in the respective year and all previous years. Incident asthma was defined as positive if a participant fulfilled the criteria for asthma for the first time and was negative for all previous follow-ups. Data for participants with missing information for one or more follow-ups were right censored, and incident asthma was defined missing from the first follow-up with missing data onwards.

2.4. Covariates

For reasons of consistency and comparability, we included the same set of covariates as in previous analyses of the association between air pollution and asthma incidence within the same population (Gehring et al., 2020), namely 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), mold/dampness at home, use of gas for cooking. These potential confounders have been selected *a priori* based on the literature. More details on covariates are provided in the online supplement. In addition, we explored potential confounding by neighborhood socio-economic status (SES) using the status scores of the four-digit postal code areas from The Netherlands Institute for Social Research for the years 1998-2017. The status scores include the average income, the percentage of residents with a low income, the percentage of unemployed persons, and the percentage of low-educated residents in a postal-code area. Lower status scores indicate lower neighborhood SES (Sociaal en Cultureel Planbureau SCP, 2006).

2.5. Statistical analysis

Categorical variables were presented as numbers (proportions), continuous variables were presented as means with standard deviation.

Correlations between different air pollutants and correlations between UFP exposures at different follow-up periods were presented as Spearman correlation coefficients. Associations of UFP exposure with asthma incidence from birth until age 20 years were analyzed using discrete-time hazard models (Singer and Willett, 2003), dividing the follow-up from birth until age 20 into 12 discrete periods (that is eight periods of one year and four periods of three years) in between questionnaires and modelling 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 for all time periods and more recent exposure at a specific follow-up for the respective period. All analyses were performed with and without adjustment for the covariates described above.

To explore the shape of the concentration-response curve, we applied natural splines with three to six degrees of freedom in the adjusted model and tested for linearity by comparing the models with and without splines using the likelihood ratio test. The results were the same for the different spline models (data not shown), and therefore, we present the simplest model (with three degrees of freedom) in Fig. 1. Sex- and age-specific association estimates were obtained from main effects for exposure and exposure-age and exposure-sex interaction terms of models with exposure-sex and exposure-age interactions added, respectively. In addition, we explored potential modification of the association by SES by adding exposure-parental education interaction terms to the models. Two-pollutant models (of UFP with PM mass, $PM_{2.5}$ absorbance, or NO_2) were also performed. In sensitivity analyses, we restricted the analysis to those participants with nearly complete follow-up (at least 11 out of the 12 questionnaires) to assess potential attrition bias and assessed potential confounding by neighborhood SES by adding the status score to the adjusted models. Moreover, we restricted the analysis to data from age 4 onward to assess whether the associations were mainly driven by the high incidence before the age of 4 years and performed stratified analyses by moving (defined as any change in address since birth). We did not include early life and more recent UFP exposures into one model because that led to multicollinearity problems (variation inflation factors (VIFs) > 3). Associations were presented as odds ratios (OR) with 95% confidence intervals (CI) for an interquartile range (IQR) increase in exposure. All analyses were performed with R version 3.6.1 (R Core Team, 2019).

3. Results

The characteristics of the included participants are presented in Table 1. A total of 812 incident cases of asthma were identified, most of them before the age of 4 years (Table E2). The median (IQR) annual average UFP concentrations were 10,800 (2,342) particles/cm^3 for the birth addresses and 11,442 (3,833) particles/cm^3 for the addresses at the most recent follow-up (age 20 years). Distributions of annual average UFP concentrations across all follow-up ages were shown in Table 2.

Table 1
Characteristics of the included participants.

Characteristics	n/N (%)
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 center attendance[a]	2040/3538 (57.7)
Mother smoked during pregnancy	626/3652 (17.1)
Smoking at child's home[b]	
Early life[c]	912/3686 (24.7)
Age 20 years	186/2127 (8.7)
Active smoking at least once a week[d]	
Age 14 years	119/2431 (4.9)
Age 20 years	426/2127 (20.0)
Use of natural gas for cooking	
Early life[c]	3028/3674 (82.4)
Age 20 years	1564/2127 (73.5)
Mold/damp spots in participant's home	
Early life[c]	300/3643 (8.2)
Age 20 years	242/2127 (11.4)
Furry pets in participant's home	
Early life[c]	1720/3677 (46.8)
Age 20 years	877/2127 (41.2)

[a] During second year of life.
[b] Defined as parental smoking until and including age 17 years and any smoking at age 20 years.
[c] During first year of life.
[d] At age ≥14 years.

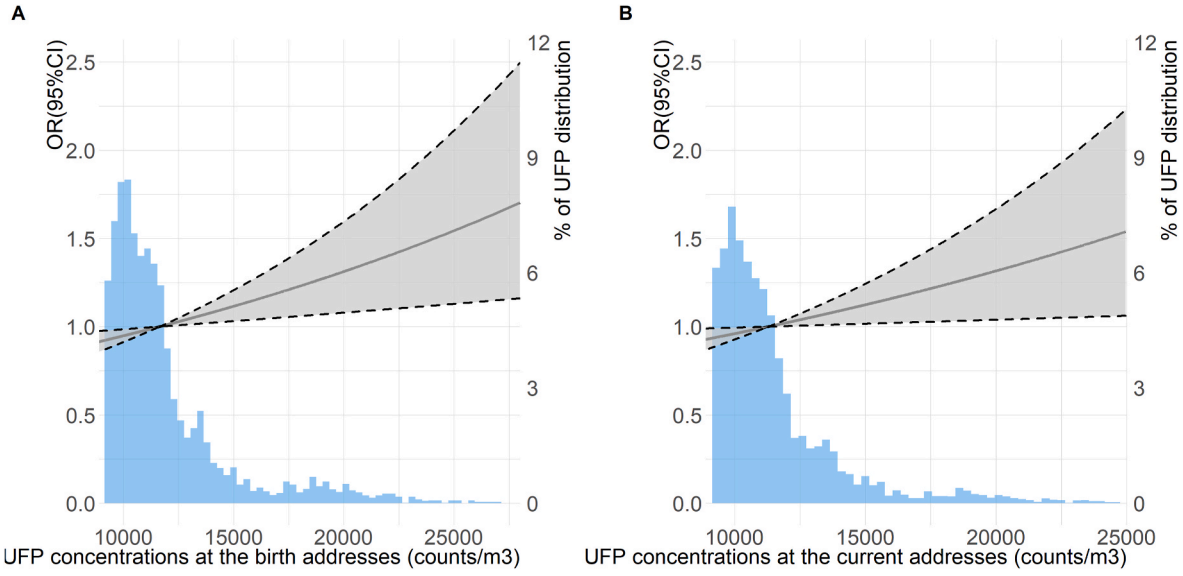

Fig. 1. Exposure-response curves using natural splines with 3 degrees of freedom for the associations of ultrafine particle (UFP) exposure early in life (i.e. at the birth address) and more recently (i.e. at the current address at the time of the follow-up) with asthma incidence until age 20 years*.
* 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), mold/dampness at home, use of gas for cooking.

Table 2
Distribution of ultrafine particle (UFP) concentrations at the birth address and home addresses at different follow-ups.

Follow-ups	UFP concentration (particles/cm^3)						
	Min	25th percentile	Median	75th percentile	Maximum	Mean ± Std	IQR
Birth address	8598	9861	10,800	12,203	44,578	11,716 ± 2645	2342
Age 1	8598	9859	10,829	12,150	36,167	11,656 ± 2965	2291
Age 2	8598	9792	10,717	11,949	36,167	11,486 ± 2849	2157
Age 3	8598	9770	10,672	11,916	36,167	11,385 ± 2708	2146
Age 4	8598	9722	10,593	11,808	36,167	11,246 ± 2541	2086
Age 5	8598	9689	10,551	11,730	36,167	11,191 ± 2494	2041
Age 6	8598	9670	10,522	11,677	36,167	11,158 ± 2479	2007
Age 7	8598	9651	10,496	11,640	36,167	10,496 ± 2422	1989
Age 8	8598	9644	10,485	11,618	36,167	11,077 ± 2343	1974
Age 11	8586	9566	10,419	11,557	31,423	10,419 ± 2234	1991
Age 14	8598	9569	10,412	11,489	31,423	10,924 ± 2142	1920
Age 17	8598	9566	10,425	11,523	31,423	10,969 ± 2221	1957
Age 20	8598	10,013	11,442	13,846	40,241	12,467 ± 3595	3833

Note: Std, Standard deviation; IQR, interquartile range.

Correlations between estimated UFP levels at the birth addresses and addresses at the different follow-ups ranged from 0.97 at age 1 to 0.61 at age 17 years and decreased further to 0.41 at 20 years (Figure E1). Correlations with estimated annual average UFP levels were high for NO_2, $PM_{2.5}$ absorbance, PM_{coarse} and PM_{10} (r = 0.80 to 0.85), and moderate for $PM_{2.5}$ (r = 0.57, Figure E2).

Exposure-response analysis showed a generally linear association between both early life and more recent UFP exposure and asthma incidence (Fig. 1). Overall, we observed higher odds of incident asthma with both early life and more recent UFP exposure in the crude models (OR (95% CI) 1.07 (1.02,1.12) and 1.06 (1.00, 1.11) per IQR increase in early life and more recent exposure, respectively; Table 3). The association estimates were essentially the same after adjustment for potential confounders (1.08 (1.02, 1.12) and 1.06 (1.00, 1.12) for early life and more recent exposure, respectively).

No consistent patterns and wider confidence intervals were observed for age-specific associations (Fig. 2). In the sex-specific analysis, the association estimates tended to be stronger in girls than in boys, but the UFP exposure-sex interactions were not statistically significant (P for interaction 0.765 for early exposure and 0.871 for more recent exposure). Restricting our analysis to data up to age 12 also generated similar results (Table E3).

For early-life UFP exposure, sensitivity analyses restricted to data from age 4 onwards generated similar association estimates, but wider confidence intervals due to the smaller number of cases. Associations were still positive when we restricted to nearly 1700 subjects who participated in at least 11 of the 12 follow-ups. Results for more recent exposure were less stable compared with the association of early life exposure, and associations remained largely unchanged when we additionally adjusted for neighborhood SES (Table E4). Associations with both early life and more recent exposure tended to be stronger in non-movers than on movers, but differences were not significant with confidence intervals overlapped (Table E5). Associations were also slightly stronger among children of parents with a low or medium level of education compared to children of highly educated parents, but the differences were not significant (Table E6).

In two-pollutant models adjusting for $PM_{2.5}$ or PM_{10}, the estimates for UFP remained similar to those from single pollutant models (OR (95%CI) 1.06 (0.99, 1.13) and 1.07 (0.97, 1.17) for early life UFP exposure, 1.06 (0.97, 1.13) and 1.05 (0.95, 1.15) for more recent UFP exposure after adjusting for $PM_{2.5}$ and PM_{10}, respectively) while the estimates for $PM_{2.5}$ or PM_{10} generally attenuated towards the null. In two-pollutant models adjusting for PM_{coarse}, NO_2, or $PM_{2.5}$ absorbance, the estimates for UFP generally diminished to null while the associations with PM_{coarse}, NO_2, and $PM_{2.5}$ absorbance persisted (Fig. 3 for early life exposure and Figure E3 for more recent exposure and Table E7 for exact numbers).

4. Discussion

Overall, we found higher UFP exposure to be associated with a higher risk of developing asthma from birth until age 20 years in the PIAMA cohort in single pollutant models. However, these associations attenuated to null after adjusting for NO_2, $PM_{2.5}$ absorbance or PM_{coarse}. Age-specific associations with UFP were less consistent than those with NO_2 and $PM_{2.5}$ absorbance reported previously.

This study extends our previous analyses within the PIAMA birth cohort on the association of regulated outdoor air pollution exposure with asthma development from birth up to the age of 20 years (Gehring et al., 2020). To date, only few studies reported on the association between long-term UFP exposure and asthma development in children (Wright et al., 2021; Lavigne et al., 2019). In a retrospective cohort of 160,641 children from Toronto, Canada, prenatal exposure to UFP was associated with a higher risk of asthma onset before age 6 (Lavigne et al., 2019). Another study was based on linkage of 376 mother-child pairs (69 children developed asthma) from the northeastern US with a spatial-temporal UFP exposure model (Simon et al., 2020) and found that prenatal exposure to UFP was positively associated with childhood asthma incidence (Wright et al., 2021). However, there were noteworthy differences between these two studies and the current study. In

Table 3
Crude and adjusted[a] odds ratios (OR) with 95% confidence intervals (95% CI) for the overall associations of annual average ultrafine particle 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.

Exposure		Crude			Adjusted[a]		
Timing	Increment	N[b]/Cases	OR[c] (95%CI)	P-value	N[b]/Cases	OR[c] (95%CI)	P-value
Birth address	2342 particles/cm^3	3674/805	1.07 (1.02, 1.12)	0.008	3159/545	1.08 (1.02, 1.14)	0.008
Current address	2129 particles/cm^3	3686/812	1.06 (1.00, 1.11)	0.034	3168/547	1.06 (1.00, 1.12)	0.052

[a] 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), mold/dampness at home, use of gas for cooking.
[b] Total number of cases.
[c] ORs (95%CI) are presented for an interquartile range increase in exposure.

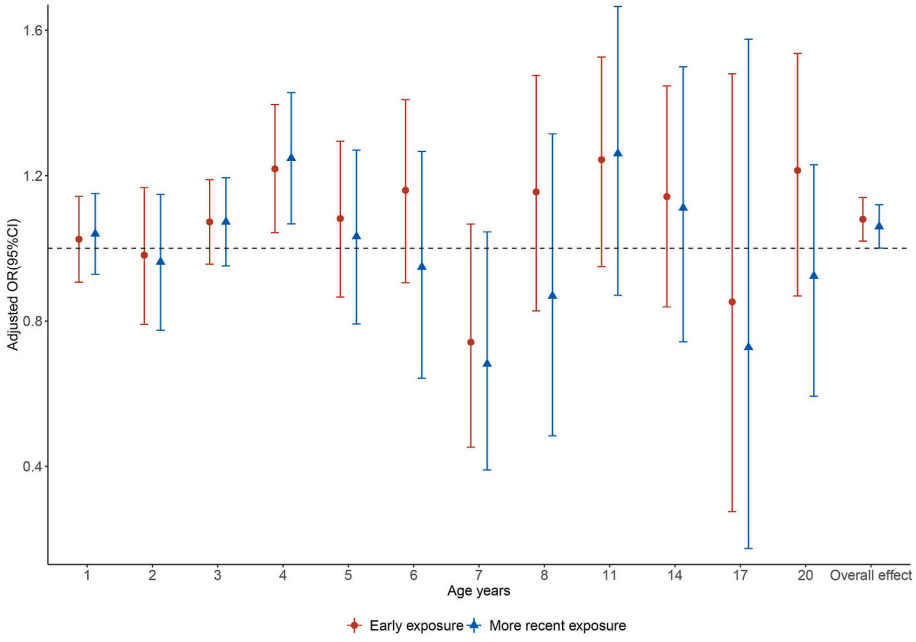

Fig. 2. Adjusted* age-specific associations of ultrafine particle exposure (per interquartile range increase) early in life (i.e. at the birth address) and more recently (i.e. at the current address of the follow-up) with asthma incidence until age 20 years.
* Adjusted for sex, maternal and paternal 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), mold/dampness at home, use of gas for cooking.

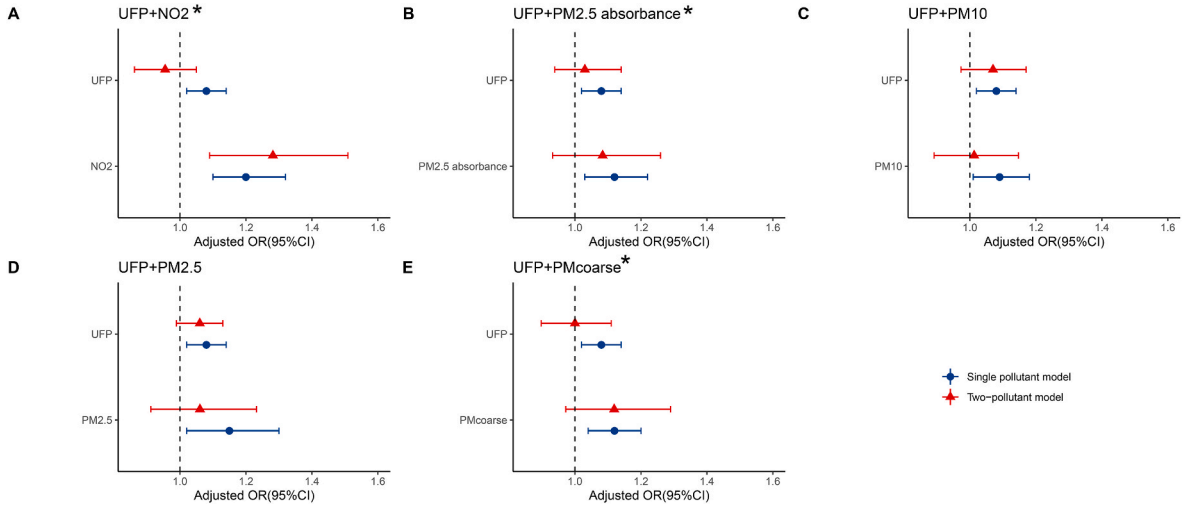

Fig. 3. Adjusted† associations of ultrafine particle (UFP) exposure (per interquartile range increase) in early life (i.e. at the birth address) with asthma incidence until age 20 years in single pollutant and two-pollutant models. Panel A: UFP and nitrogen dioxide (NO_2); panel B: UFP and particulate matter with a diameter <2.5 μm ($PM_{2.5}$) absorbance; panel C: UFP and particulate matter with a diameter <10 μm (PM_{10}); panel D: UFP and $PM_{2.5}$; panel E: UFP and particulate matter with a diameter 2.5–10 μm (PM_{coarse}).
* Variance inflation factors ranging from 3.21 to 3.82. All other variance inflation factors were below 3.
† 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), mold/dampness at home, use of gas for cooking.

the Canadian study for example, Lavigne and colleagues developed an UFP LUR model (Weichenthal et al., 2016) for Toronto, Ontario, Canada based on mobile monitoring data only (two weeks in September 2010 and one week in March 2011 focused on rush hours: 7:00–10:00 in the morning and 15:00–18:00 in the afternoon). In the US study, Wright and colleagues applied a daily spatial-temporal UFP model (Simon et al., 2020) that combines fixed-site and mobile monitoring data (4–6 h shifts between 05:00 and 21:00 h on all days of the week and in all seasons). In our study, the mobile UFP monitoring data were collected avoiding the rush hours to increase the comparability of measurements between sites, which may result in different exposure contrasts compared with those monitoring on all days. However, in the Netherlands we have previously demonstrated high correlations ($R^2 > 0.95$) between UFP concentrations measured at different times of the day including rush hours, daytime non-rush hours and 24-h averages, and reported small differences between the 24-h average concentrations and the average of the period used for the mobile monitoring for this study (Downward et al., 2018). The differences in mobile monitoring strategy may partly explain the differences in estimated UFP concentrations levels between the three studies (highest in Toronto, lowest in the Netherlands) since motor traffic is considered a major source of ambient UFP.

In the Canadian study, UFP exposure was not correlated with NO_2 and in the US study, correlation was moderate between UFP and NO_2 exposure estimates (Spearman correlation $r_s = 0.68$, 0.60 and 0.69 for 1st, 2nd and 3rd trimesters, respectively), while in our study the correlation was relatively high between UFP and NO_2 exposure ($r = 0.81$ at

the birth address), which may in part be explained by differences in air pollution sources between different study areas. Both the Canadian study and US study suggest independent associations of prenatal UFP exposure over $PM_{2.5}$ and NO_2 on asthma development with different critical exposure windows identified (second trimester in the Canadian study and third trimester in the US study). With a different focus on exposure period and a much longer follow-up, what the current study adds to the previous two studies is that exposure to UFP early in life may have long-term consequences for asthma development not only in childhood, but also into adolescence and early adulthood.

It remains challenging to disentangle the contribution of UFP from other traffic-related air pollutants such as NO_2 and $PM_{2.5}$ absorbance due to the high correlations between the pollutants. In the current study, we used a standard two-pollutant model, which included both UFP and another air pollutant. However, two-pollutant model results can be hard to interpret when the two pollutants in a model reflect the same source (i.e. UFP, $PM_{2.5}$ absorbance, and NO_2 share traffic as a major source). An additional complication of the two-pollutant model with UFP and $PM_{2.5}$ absorbance is that $PM_{2.5}$ absorbance contains a large proportion of UFP. The association estimates for UFP remained largely unchanged in two-pollutant models with $PM_{2.5}$ and PM_{10}, but confidence intervals for UFP became wider, supporting a more important role of traffic-related air pollutants in the impact of outdoor air pollution on asthma development. In contrast, the association estimates for UFP turned to unity while the estimates for PM_{coarse} remained largely unchanged in the UFP + PM_{coarse} model. The predictors selected into the LUR model of PM_{coarse} include both traffic -(traffic load in a buffer of 1000 m and traffic intensity on the nearest load) and non-traffic sources (ports within a buffer of 5000 m) indicating that traffic may not be the only important source of air pollution that is relevant for asthma development.

Strengths of the present study are the prospective study design, the availability of residential and exposure histories since birth, and the adjustment for a multitude of potential confounding factors. A potential limitation of our study is that our UFP exposure models are purely spatial and do not account for temporal trends, due to very limited historical data for UFP. We used a spatial UFP model that was developed based on measurement campaigns performed in 2016–2017 to predict exposure over a period of 20 years starting from 1996/1997. Some support for the stability of spatial contrasts in UFP levels is provided by a comparison of modeled concentrations with independent longer-term UFP measurements in Amsterdam and Utrecht from 2014 ($R^2 = 0.6$) (Kerckhoffs et al., 2021). Spatial contrasts in measured and modeled annual average NO_2 levels have been shown to be stable over periods of 7–12 years (Weichenthal et al., 2016; Downward et al., 2018; Cesaroni et al., 2012; Eeftens et al., 2011; Gulliver et al., 2011, 2013; Wang et al., 2013). Given the very high correlation between UFP and NO_2 in the current study, spatial contrast in UFP concentrations can also be assumed to be stable over time. No information is available about the sensitivity and specificity of the asthma definition that has been used and that relies on parental and self-reported diagnosis, symptoms and medication use. Misclassification bias is therefore a potential concern. Since information regarding air pollution exposure levels has not been shared with the participants and their doctors, outcome misclassification bias (if any) is likely non-differential and towards the null. Outcome misclassification may more of a concern at younger ages as asthma is difficult to diagnose in very young children. A large portion of the asthma cases in this cohort was identified before the age of 4 years. However, a sensitivity analysis restricted to data from age 4 onwards in the current cohort yielded similar association estimates, indicating that the observed association in the main analysis were not driven by associations with asthma diagnoses at ages 4 and younger. Consistent with earlier findings for other pollutants in our cohort (Gehring et al., 2020), also in the current study, the association estimates tend to be more stable for early life exposure than for more recent exposure. But it remains unclear whether early-life exposure to UFP is more relevant for asthma development than more recent exposure, as the UFP concentrations at the birth address and follow-up addresses are highly correlated for most of the follow-ups (Figure E1) and multicollinearity problems occurred when including exposures for the two different time windows into one model. Larger cohorts with spatial-temporal air pollution models are needed for these analyses. We also acknowledge that we lack the power to detect any sex-specific effect of UFP exposure on asthma development during and after puberty due to the small number of cases at that period (Table E2). Larger cohorts and/or analyses within multiple cohorts are needed for this purpose.

In conclusion, our findings support the important role of traffic-related air pollutants in asthma development, but provide little evidence for an independent effect of UFP.

Authors' contributions

UG designed the study. ZY and UG had full access to all data in the study. ZY carried out the statistical analysis and wrote the initial draft of the manuscript. JK, GH, RV and UG contributed UFP exposure assessment. GK, RV and UG secured funding. All authors (i) provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, (ii) revised the manuscript for important intellectual content, (iii) approved the final version, and (iv) agreed to be accountable for all aspects of the work.

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Ethics approval

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.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gerard H. Koppelman reports a relationship with GSK that includes: consulting or advisory. Gerard H.Koppelman reports a relationship with PURE IMS that includes: consulting or advisory.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113770.

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