

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 NO₂ 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}, PM₁₀, and PM_{coarse} (PM₁₀-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 R²) 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 R², selected the one giving the highest gain in adjusted R², 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 R² of the previous model. Model performance was generally good (leave one out cross-validation R²=61-89%, Table E1), but lower for PM_{coarse} (38%).

References

1. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, Declercq C, Dedele A, Dons E, de Nazelle A, Dimakopoulou K, Eriksen K, Falq G, Fischer P, Galassi C, Grazuleviciene R, Heinrich J, Hoffmann B, Jerrett M, Keidel D, Korek M, Lanki T, Lindley S, Madsen C, Molter A, Nador G, Nieuwenhuijsen M, Nonnemacher M, Pedeli X, Raaschou-Nielsen O, Patelarou E, Quass U, Ranzi A, Schindler C, Stempfelet M, Stephanou E, Sugiri D, Tsai MY, Yli-Tuomi T, Varro MJ, Vienneau D, von Klot S, Wolf K, Brunekreef B, Hoek G. Development of Land Use Regression Models for PM_{2.5}, PM_{2.5} Absorbance, PM₁₀ and PM_{coarse} in 20 European Study Areas; Results of the ESCAPE Project. *Environ Sci Technol* 2012; 46(20): 11195-11205.
2. Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, Tsai MY, Kunzli N, Schikowski T, Marcon A, Eriksen KT, Raaschou-Nielsen O, Stephanou E, Patelarou E, Lanki T, Yli-Toumi T, Declercq C, Falq G, Stempfelet M, Birk M, Cyrus J, von Klot S, Nador G, Varro MJ, Dedele A, Grazuleviciene R, Molter A, Lindley S, Madsen C, Cesaroni G, Ranzi A, Badaloni C, Hoffmann B, Nonnemacher M, Kraemer U, Kuhlbusch T, Cirach M, de Nazelle A, Nieuwenhuijsen M, Bellander T, Korek M, Olsson D, Stromgren M, Dons E, Jerrett M, Fischer P, Wang M, Brunekreef B, de Hoogh K. Development of NO₂ and NO_x land use regression models for estimating air pollution exposure in 36 study areas in Europe - The ESCAPE project. *Atmos Environ* 2013; 72: 10-23.

Table E1. Land-use regression models with model R².

Pollutant	Land-use regression model	Model R ²	LOOCV R ²
NO ₂	$-7.80 + 1.18 \times \text{REGIONALESTIMATE} + 2.30 \times 10^{-5} \times \text{POP_5000} + 2.46 \times 10^{-6} \times \text{TRAFLOAD_50} + 1.06 \times 10^{-4} \times \text{ROADLENGTH_1000} + 9.84 \times 10^{-5} \times \text{HEAVYTRAFLOAD_25} + 12.19 \times \text{DISTINVNEARC1} + 4.47 \times 10^{-7} \times \text{HEAVYTRAFLOAD_25_500}$	86%	81%
PM _{2.5} absorbance	$0.07 + 2.95 \times 10^{-9} \times \text{TRAFLOAD_500} + 2.93 \times 10^{-3} \times \text{MAJORROADLENGTH_50} + 0.85 \times \text{REGIONALESTIMATE} + 7.90 \times 10^{-9} \times \text{HLDRES_5000} + 1.72 \times 10^{-6} \times \text{HEAVYTRAFLOAD_50}$	92%	89%
PM _{2.5}	$9.46 + 0.42 \times \text{REGIONALESTIMATE} + 0.01 \times \text{MAJORROADLENGTH_50} + 2.28 \times 10^{-9} \times \text{TRAFMAJORLOAD_1000}$	67%	60%
PM ₁₀	$23.71 + 2.16 \times 10^{-8} \times \text{TRAFMAJORLOAD_500} + 6.68 \times 10^{-6} \times \text{POP_5000} + 0.02 \times \text{MAJORROADLENGTH_50}$	68%	61%
PM _{coarse}	$7.59 + 5.02 \times 10^{-9} \times \text{TRAFLOAD_1000} + 1.38 \times 10^{-7} \times \text{PORT_5000} + 5.38 \times 10^{-5} \times \text{TRAFNEAR}$	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).

Variable	All participants		20-year follow-up	
	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/m ³]	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/m ³]	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/m ³]	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/m ³]	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/m ³]	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/m ³]	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/m ³]	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/m ³]	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.

Pollutant [increment]	Adjusted		
	OR	(95% CI)	p-value
Current address			
N=3,181 subjects			
NO ₂ [9.2 µg/m ³]	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/m ³]	1.19	(1.04-1.35)	0.0106
PM ₁₀ [1.2 µg/m ³]	1.07	(0.99-1.17)	0.0919
PM _{coarse} [0.9 µg/m ³]	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/m ³]	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/m ³]	1.15	(0.95-1.39)	0.1419
PM ₁₀ [1.2 µg/m ³]	1.09	(0.97-1.22)	0.1295
PM _{coarse} [0.9 µg/m ³]	1.13	(1.02-1.26)	0.0240
Current address			
N=3,564 subjects			
NO ₂ [9.2 µg/m ³]	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/m ³]	1.22	(0.99-1.51)	0.0611
PM ₁₀ [1.2 µg/m ³]	1.05	(0.92-1.20)	0.4663
PM _{coarse} [0.9 µg/m ³]	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.

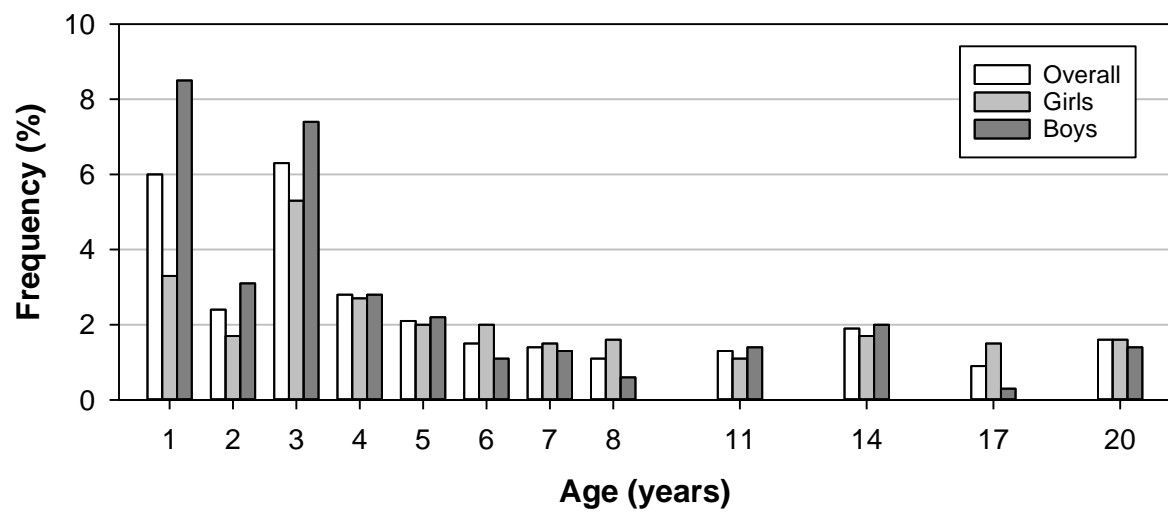


Figure E2. Heatmap of Spearman correlations between air pollutants and follow-ups.

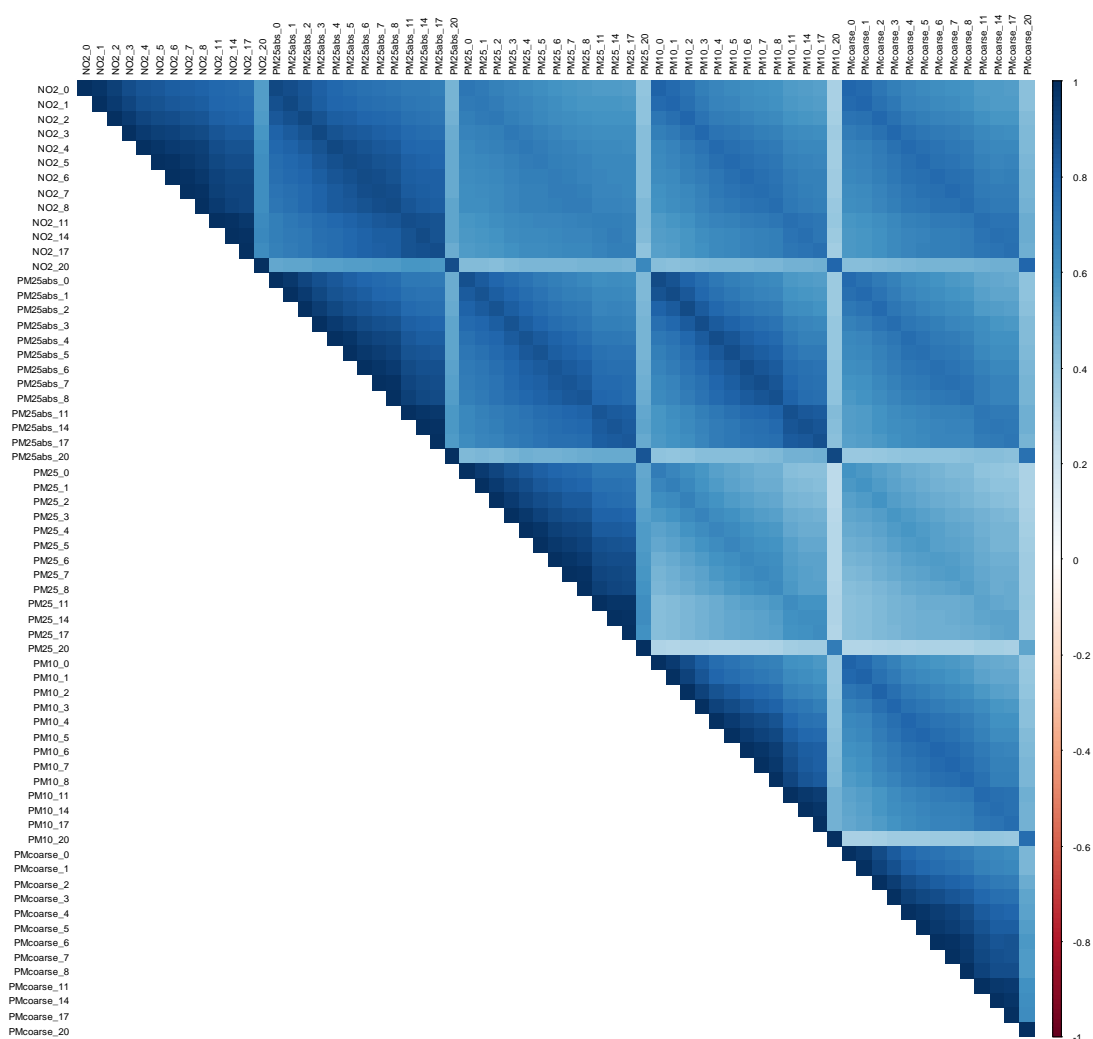
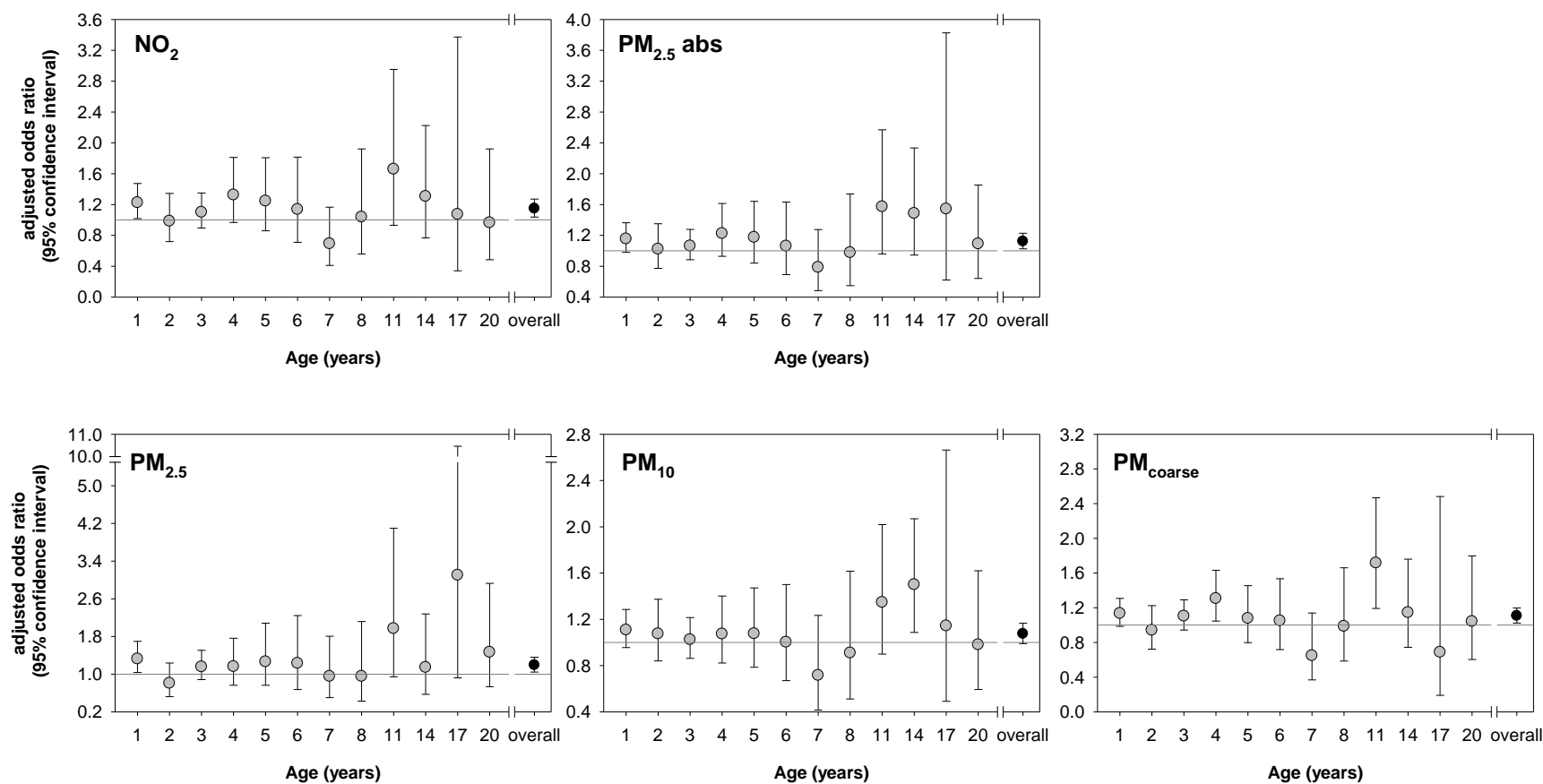
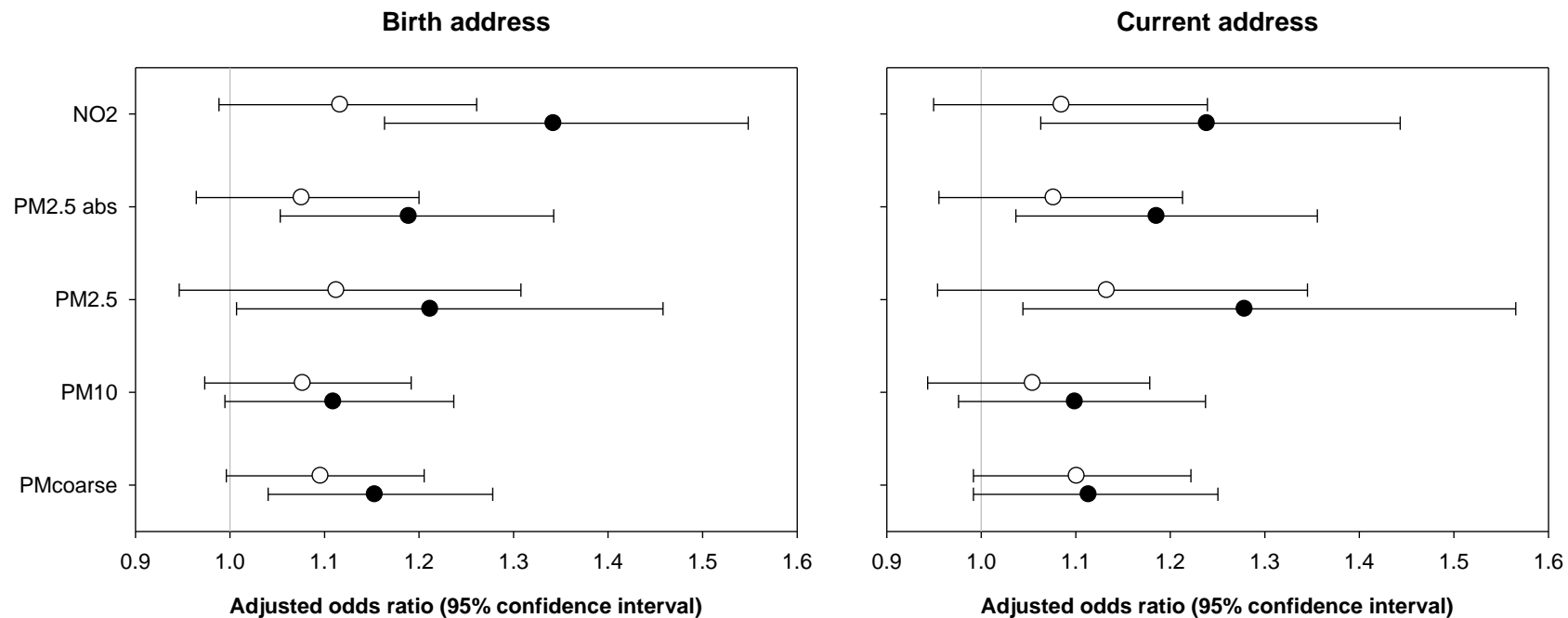


Figure E3. Adjusted* age-specific associations of more recent air pollution exposure (i.e. at the current address at the time of follow-up) with asthma incidence until age 20 (N=3,181 subjects).



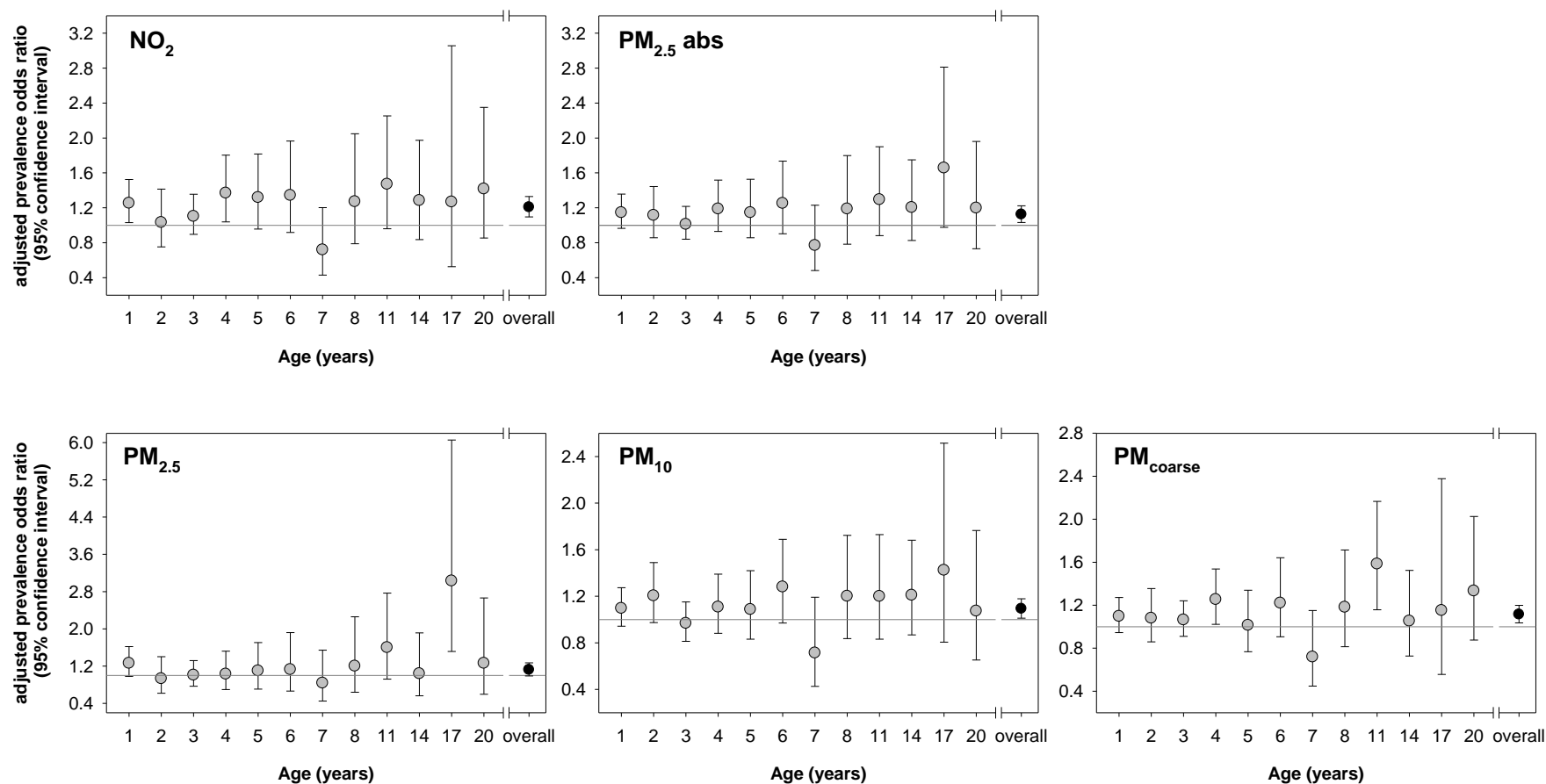
* adjusted for maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

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).



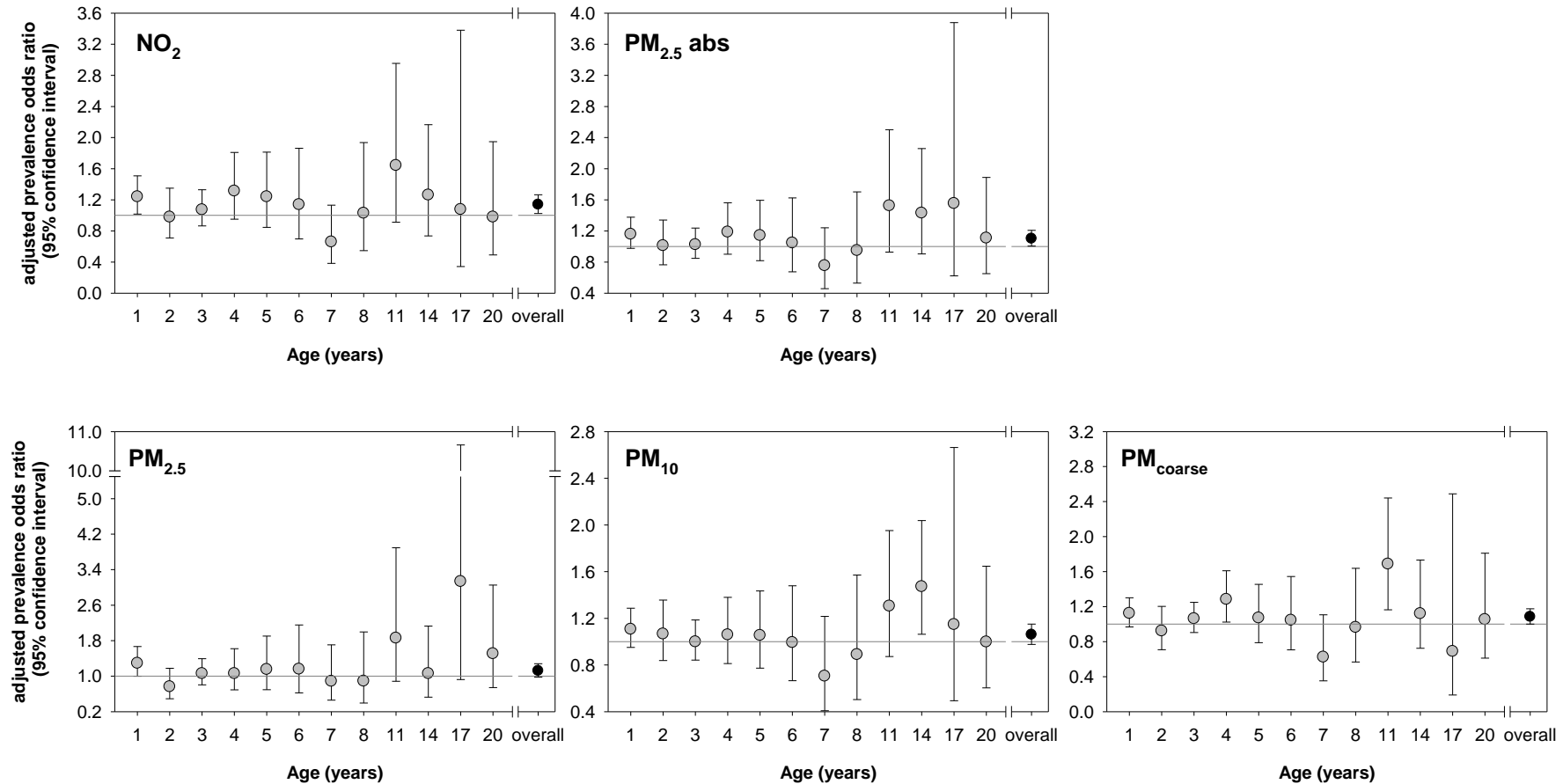
* adjusted for age, maternal and paternal asthma and/or hay fever, Dutch nationality, parental education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home, active smoking (from age 14), mold/dampness at home, pets, use of gas for cooking

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