

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Prenatal particulate matter affects new asthma via airway hyperresponsiveness in schoolchildren

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Abstract

Background: The most relevant time of PM₁₀ exposure to affect airway hyperresponsiveness (AHR) and new development of asthma in school-aged children is unclear. The aims of this study were to investigate the most critical time of PM₁₀ exposure to affect AHR and new diagnosis of asthma from AHR in school-aged children.

Methods: Elementary schoolchildren (n = 3570) have been enrolled in a nationwide prospective 4-year follow-up survey in Korea from 2005 to 2006. Individual annual PM₁₀ exposure was estimated by using an ordinary kriging method from the prenatal period to 7 years of age. AHR at 7 years was defined by a methacholine PC₂₀ ≤ 8 mg/mL.

Results: PM₁₀ exposure during pregnancy and at 1 year of age showed significant effects on AHR (aOR: 1.694, 95% CI: 1.298–2.209; and aOR: 1.750, 95% CI: 1.343–2.282, respectively). PM₁₀ exposure during pregnancy was associated with the risk of a new diagnosis of asthma (aOR: 2.056, 95% CI: 1.240–3.409), with the highest risk in children with AHR at age 7 (aOR: 6.080, 95% CI: 2.150–17.195). PM₁₀ exposure in the second trimester was associated with the highest risk of a new diagnosis of asthma in children with AHR at age 7 (aOR: 4.136, 95% CI: 1.657–10.326).

Conclusions: Prenatal PM₁₀ exposure in the second trimester is associated with an increased risk of a new diagnosis of asthma in school-aged children with AHR at 7 years. This study suggests that PM₁₀ exposure during a specific trimester in utero may affect the onset of childhood asthma via AHR.

KEYWORDS

airway hyperresponsiveness, asthma, children, Particulate matter, prenatal

1 | INTRODUCTION

Airway hyperresponsiveness (AHR) is not only an important feature of symptomatic asthma, but also a predictive factor for future asthma.^{1–4} However, not all individuals with asymptomatic AHR develop asthma.⁵ Several determinants, such as age, sex, atopic status, genetic susceptibility, and environmental exposures, may be associated with asthma development.⁶ Although previous studies have reported an association between AHR and a new diagnosis of asthma, relatively little is known about the environmental factors affecting AHR. Furthermore, the environmental factors that increase the risk of a new diagnosis of asthma in children with asymptomatic AHR remain unclear. Hence, it is important to determine the environmental factors affecting AHR and the association between AHR and new diagnosis of asthma.

Particulate matter (PM) has been suggested to play a role in asthma development and lung function impairment in children.^{7–11} The prenatal and early childhood periods are considered to be critical times for the effects of PM on the development of respiratory systems and later respiratory outcomes (eg, lung function, asthma, and chronic obstructive pulmonary diseases).¹² However, studies to date that compared different time periods on the effects of PM in childhood asthma have reported inconsistent results.^{9,13–15} Notably, in this regard, prior reports that have evaluated the critical period during pregnancy in which PM exposure produces a higher risk of asthma development are scarce. One such study did report that PM_{2.5} exposure during the 16- to 25-week gestation period was associated with preschool asthma onset by age 6.¹⁶ However, no studies to date have evaluated the critical PM exposure time for asthma development in school-aged children in relation to AHR.

We thus aimed in our present study to investigate the most critical timing at which PM exposure leads to AHR and to evaluate the effect and critical period of PM exposure that gave the highest risk of a new diagnosis of asthma in children with AHR at age 7.

2 | METHODS

2.1 | Subjects and study design

This study was conducted as part of the Children's HEalth and Environmental Research (CHEER) study performed in 10 cities in Korea: Seoul, Daegu, Busan, and Kwangju (urban areas); Incheon, Yeosu, and Mokpo (industrial areas); and Cheonan, Jeju, and Jeongeup (rural areas). A total cohort of 3570 elementary schoolchildren was recruited from 2005 to 2006 and followed up 4 years later (Figure 1).

The participants' parents were asked to complete the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to evaluate the presence of allergic diseases and risk factors.^{17,18} Written consent was obtained from the parents of all participants after they were fully informed of the details of the study. The study protocol was approved by the institutional review board of the University of Ulsan College of Medicine (IRB no. 2006–0081).

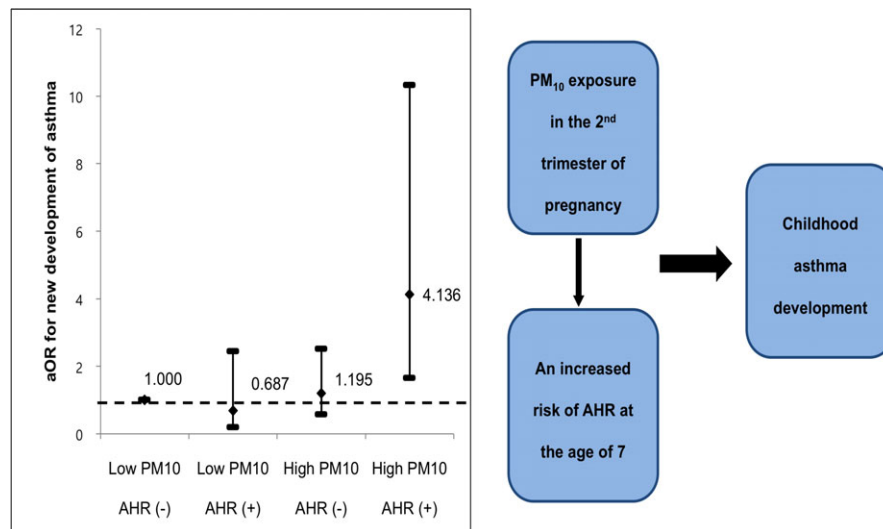
2.2 | Exposure assessments

We calculated the weekly mean concentrations of prenatal PM₁₀ and the annual mean concentrations of postnatal PM₁₀ at the individual level using ordinary kriging methods as previously described.^{19,20} The PM₁₀ levels were obtained from air monitoring data collected at monitoring stations operated by the Department of Environment, Republic of Korea, from 1997 to 2005.²¹ From 11 to 27 monitoring stations were established in each of the 10 cities where the participants were enrolled. All participant addresses from birth to 7 years of age were collected by questionnaire and geocoded. If the address of the subject had changed during the exposure period, the new address was used in the assessment of the PM₁₀ exposure. The mean PM₁₀ concentrations at the individual level were assessed using ordinary kriging methods implemented with the geostatistical analyst extension of Arc-GIS (Arc-Map, version 9.3; ESRI Inc, Redlands, WA).²⁰ Kriging is a weighted combination of values from monitored locations and uses spatial autocorrelation among groups of data to determine the weights. We evaluated the quality of the calculated values from kriging using cross-validation. To compare the effect of exposure time, we calculated the mean PM₁₀ concentrations each year from the prenatal period to 7 years of age.

The prenatal period was divided into three trimesters: from week 1 to 13 (first), week 14 to 27 (second), and from week 28 to week 40 (third).²² Lifetime exposure was defined as the overall exposure to PM₁₀ from the prenatal period to 7 years of age and was estimated using annual mean concentrations. PM₁₀ concentrations were log-transformed and dichotomized using the median concentration as either "high" or "low" exposure. These dichotomous concentrations were used to determine the effect of PM₁₀ on AHR and asthma.

2.3 | Assessment of asthma

Asthma was assessed using the following question: "Has your child been diagnosed with asthma by a physician at any time during his/her lifetime?" ("asthma diagnosis ever"). Current asthma was defined



GRAPHICAL ABSTRACT

Higher PM₁₀* exposure in the second trimester and AHR[#] at 7 years showed combined effect on the new diagnosis of asthma at school age (aOR 4.136). PM₁₀* exposure in the second trimester may affect the development of childhood asthma via AHR[#]. *PM₁₀: Particulate matter with an aerodynamic diameter of less than 10 μ m. [#]AHR: Airway hyperresponsiveness.

as an asthma diagnosis at any time and the occurrence of asthmatic symptoms within the previous 12 months. Children with no history of asthma at the first survey but who subsequently reported an asthma diagnosis at the follow-up survey were classified as having a new diagnosis of asthma.^{17,18}

2.4 | Airway hyperresponsiveness measurements using a methacholine challenge test

AHR was measured twice (at study enrollment and at the 4-year follow-up) with a methacholine challenge test using a modification of the method described by Chai et al.²³ The methacholine challenge test was performed in 1644 children at study enrollment. Among these subjects, 920 children were followed up 4 years later and 872 children underwent the methacholine challenge test at that follow-up survey (Figure 1). The methacholine PC₂₀ cutoff value for confirming AHR at 7 years of age is unknown at present. For evaluating the effect of PM₁₀ on AHR and further asthma development, we considered a methacholine PC₂₀ value of ≤ 8 mg/ml to be indicative of AHR.²⁴ A new diagnosis of AHR was defined by a positive conversion from a PC₂₀ > 8 mg/ml at the first survey. The methacholine challenge test is further detailed in the online repository.

2.5 | Skin prick test

Skin prick tests were performed at study enrollment using 18 common Korean inhalants and food allergens, together with negative and positive controls (Allergopharma, Reinbek, Germany).¹⁹ These allergens included *Dermatophagoides pteronyssinus* and

Dermatophagoides farinae, cockroach, grass, tree mix (I), tree mix (II), mugwort, ragweed, oak, alder, cat, dog, *Alternaria alternata*, *Aspergillus fumigatus*, egg, milk, peanut, and soybean. A mean wheal diameter of at least 3 mm greater than the negative control was considered to be a positive result. Atopy was defined as the presence of one or more positive reactions via the skin prick test.

2.6 | Statistical analysis

The associations between PM₁₀ and AHR/asthma were analyzed using multiple logistic regressions, and the results were expressed as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Adjustments were made for age, sex, body mass index (BMI), pre-term birth, birthweight, maternal education level, environmental tobacco smoke (ETS), and parental history of allergic diseases. Binary comparisons were made using the Student *t* test for continuous

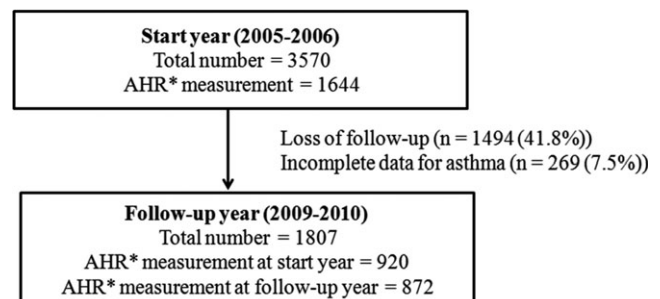


FIGURE 1 Study population. *AHR, airway hyperresponsiveness

TABLE 1 Characteristics of the study population (n = 3570)

	n	%
Age (year, mean $\pm$ SD)	7.5 $\pm$ 0.5	
Male	1849/3,570	51.8
Body mass index (kg/m ²) ^a	3233	
Normal	2630	81.4
Overweight	340	10.5
Obesity	263	8.1
Parental history of allergic disease	1090/3355	32.5
Maternal educational level (≥ 16 years)	1360/3470	39.2
Prematurity ^b	144/3443	4.2
Low birthweight infants ^c	118/3311	3.6
ETS ^d exposure at first survey	1031/3475	29.7
AHR ^e	358/1644	21.8
Current asthma ^f	201/3532	5.7
Atopy ^g	395/1128	35.0

^aNormal, BMI <85th percentile; overweight, 85th percentile $\leq$ BMI <95th percentile; obesity, BMI $\geq$ 95th percentile for children of the same age and sex.

^bInfants born before 37 weeks of gestation.

^cBirthweight <2500 g.

^dETS, environmental tobacco smoke.

^eAHR, airway hyperresponsiveness defined by a PC20 $\leq$ 8 mg/mL.

^fAsthma diagnosis (+) and asthma symptoms in the prior 12 months (+)

^gPresence of one or more positive reactions via the skin prick test.

variables and chi-square analysis for categorical variables. All statistical analyses were performed using SPSS 18.0 software (SPSS Inc. Chicago, IL), with $P < 0.05$ considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the study population

Table 1 summarizes the characteristics of the study population. The mean age was 7.5 $\pm$ 0.5 years, and 51.8% of the children were male. At the first survey, 21.8% of the children had AHR and 5.7% had current asthma. Comparisons of the characteristics of the subsets of children with and without measurements of AHR and follow-up status are presented in Tables E1 and E2 in the online repository. There were no significant differences found between children with and without AHR (Table E1). Children who completed the 4-year follow-up showed significant differences in sex, BMI, and parental history of allergic diseases (Table E2). The annual concentrations of PM₁₀ were similar from the prenatal period to 7 years of age (Table E3).

3.2 | Associations between PM₁₀ exposure and AHR/asthma

Higher PM₁₀ exposure during pregnancy (aOR: 1.694, 95% CI: 1.298-2.209) and at ages 1, 2, 3, and 4 years (aOR: 1.750, 95%

CI: 1.343-2.282; aOR: 1.485, 95% CI: 1.141-1.932; aOR: 1.335, 95% CI: 1.023-1.743; and aOR: 1.401, 95% CI: 1.076-1.824, respectively) was significantly associated with AHR at the first survey (Figure 2A and Table E4). During pregnancy, a higher PM₁₀ exposure at the first trimester was significantly associated with AHR at the first survey (aOR: 1.335, 95% CI: 1.048-1.701) (Table 2). Lifetime PM₁₀ exposure was associated with AHR (aOR: 1.364, 95% CI: 1.047-1.778), but the associations between lifetime PM₁₀ and AHR were reduced and no longer statistically significant after adjustment for PM₁₀ exposure during pregnancy (aOR: 0.995, 95% CI: 0.704-1.405). The risk of asthma diagnosis ever by the year of the first survey was not associated with PM₁₀ exposure (Figure 2B and Table E5).

3.3 | Associations between PM₁₀ exposure and new diagnosis of AHR/asthma

The new diagnosis of AHR was not associated with PM₁₀ exposure after the 4-year follow-up (Figure 2C and Table E6). However, a higher PM₁₀ during pregnancy was associated with a new diagnosis of asthma after the follow-up period (aOR: 2.056, 95% CI: 1.240-3.409; Figure 2D and Table E7). During pregnancy, PM₁₀ exposures in the first and second trimester were associated with a new diagnosis of asthma (aOR: 1.859, 95% CI: 1.161-2.978 and aOR: 1.690, 95% CI: 1.047-2.730, respectively; Table 2).

3.4 | Combined effect of PM₁₀ exposure and AHR at 7 years on the new diagnosis of asthma after the 4-year follow-up

To assess the combined effect of PM₁₀ exposure and AHR at age 7 on the new diagnosis of asthma during the 4-year follow-up period, study population was stratified by PM₁₀ exposure and the AHR results at 7 years of age. This led to four groups being categorized as follows: PM₁₀ (low)/AHR (–), PM₁₀ (low)/AHR (+), PM₁₀ (high)/AHR (–), and PM₁₀ (high)/AHR (+). The risk of a new diagnosis of asthma by both higher PM₁₀ exposure and AHR at 7 years was highest for PM₁₀ exposure during pregnancy (aOR: 6.080, 95% CI: 2.150-17.195; Figure 3A and Table E8). During pregnancy, a higher PM₁₀ exposure in the second trimester interacted with an AHR at 7 years of age for a new diagnosis of asthma (aOR: 4.136, 95% CI: 1.657-10.326, p for interaction 0.001), but not in the first (aOR: 2.709, 95% CI: 1.029-7.134, P for interaction 0.390) or third trimester (aOR: 2.049, 95% CI: 0.813-5.164, P for interaction 0.210; Figure 4B and Table E9).

3.5 | Associations between PM₁₀ exposure and AHR/asthma modified by atopy and sex

A higher PM₁₀ exposure during pregnancy and at ages 1 and 2 years was associated with AHR at age 7 in children with atopy (aOR: 1.928, 95% CI: 1.157-3.212; aOR: 2.951, 95% CI: 1.769-4.924; and

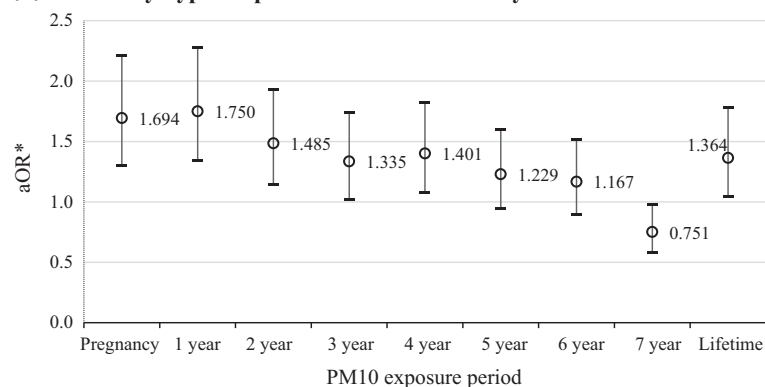
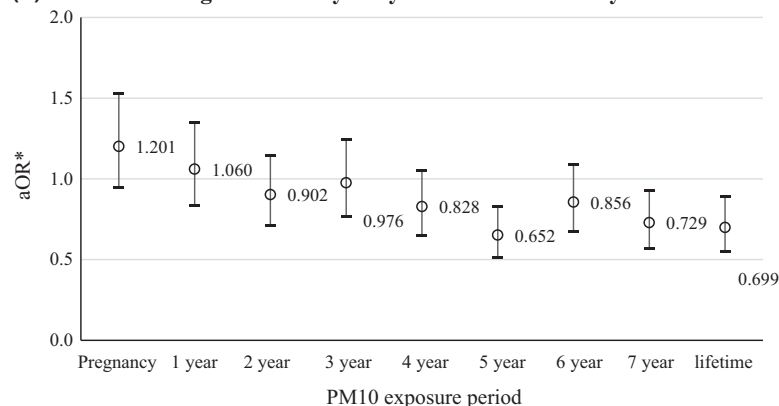
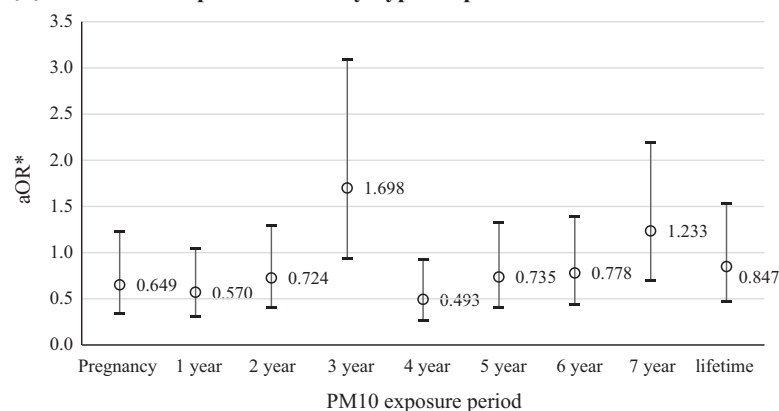
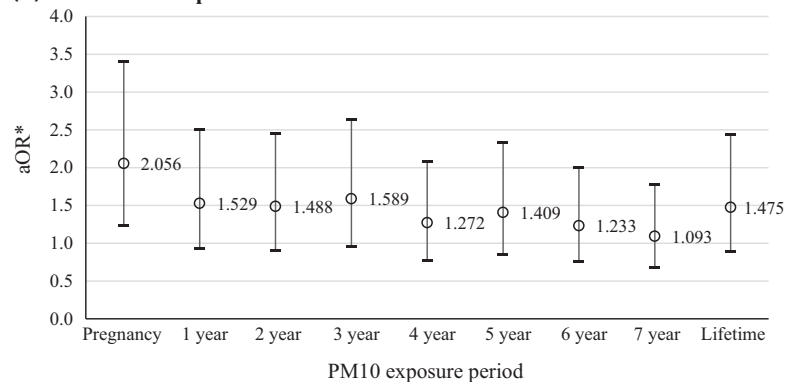
(A) Airway hyperresponsiveness at first survey**(B) Asthma diagnosis ever by the year of the first survey****(C) New development of airway hyperresponsiveness****(D) New development of asthma**

FIGURE 2 Risk of A) airway hyperresponsiveness, B) asthma diagnosis ever by the year of first survey, C) new development of airway hyperresponsiveness, and D) new development of asthma according to higher PM₁₀ exposure period. Higher PM₁₀ exposures during pregnancy and at ages 1, 2, 3, and 4 years were significantly associated with AHR at the first survey (Figure 2A). The risk of asthma diagnosis ever by the year of the first survey was not associated with PM₁₀ exposure (Figure 2B). The new diagnosis of AHR was not associated with PM₁₀ exposure after the 4-year follow-up (Figure 2C). However, a higher PM₁₀ exposure during pregnancy was associated with a new diagnosis of asthma after the follow-up period (Figure 2D). *Adjusted for age, sex, body mass index, preterm birth, birthweight, maternal education level, exposure to environmental tobacco smoke, and parental history of allergic diseases

TABLE 2 Risk of respiratory outcomes according to PM₁₀ exposure during pregnancy

	aOR ^a	95% CI		P value
AHR*by the year of first survey				
First trimester	1.335	1.048	1.701	0.019
Second trimester	1.068	0.832	1.371	0.607
Third trimester	1.109	0.866	1.419	0.412
Asthma diagnosis ever by the year of first survey				
First trimester	0.977	0.782	1.219	0.835
Second trimester	1.061	0.843	1.334	0.616
Third trimester	0.984	0.785	1.234	0.888
New development of AHR				
First trimester	1.231	0.719	2.107	0.448
Second trimester	0.823	0.471	1.441	0.496
Third trimester	0.989	0.571	1.710	0.967
New development of asthma				
First trimester	1.859	1.161	2.978	0.010
Second trimester	1.690	1.047	2.730	0.032
Third trimester	1.211	0.762	1.925	0.417

AHR, airway hyperresponsiveness.

^aAdjusted for age, sex, body mass index, preterm birth, birthweight, maternal education level, exposure to environmental tobacco smoke, and parental history of allergic diseases.

aOR: 2.043, 95% CI: 1.239-3.370, respectively; Table E10). A new diagnosis of asthma was associated with a higher PM₁₀ during pregnancy in children without atopy (aOR: 5.841, 95% CI: 1.725-19.783) (Table E10). A combined effect of PM₁₀ exposure and AHR at age 7 on the new diagnosis of asthma was highest when the exposure occurred during pregnancy in children without atopy (aOR: 31.316, 95% CI: 1.929-508.348) (Table E11).

Higher PM₁₀ exposures during pregnancy and at ages 1, 2, and 4 years were associated with AHR at age 7 in boys (Table E12). The new diagnosis of asthma was associated with PM₁₀ exposure during the second trimester and an age of 4 and 5 years in girls (Table E12). The risk of a new diagnosis of asthma in girls from both a higher PM₁₀ exposure and AHR was highest when the exposure occurred during pregnancy (Table E13).

4 | DISCUSSION

Our study results suggest that prenatal exposure to PM₁₀ had greater association with new diagnosis of asthma in school-aged children and AHR at 7 years of age than current and lifetime exposure. Furthermore, a higher prenatal PM₁₀ exposure in the second trimester and AHR at 7 years of age showed a combined effect on the new diagnosis of asthma in school-aged children. These results suggest that prenatal PM₁₀ exposure, especially in the second trimester, is associated with AHR at an early school age and the risk of new diagnosis of asthma at school age.

Although several previous studies investigated the association between PM₁₀ and development of asthma, the results have been inconsistent.⁷⁻⁹ Our present investigation differs from these previous reports in that we investigated our subjects over a large time span that included the prenatal period, we conducted our asthma assessments in cases with objectively confirmed AHR, and we performed follow-up studies in the schoolchildren we analyzed. Hence, we could demonstrate a clearer relationship between asthma development and early-life PM₁₀ exposure.

AHR is an important intermediate phenotype of asthma and may provide key insights into its underlying pathophysiology. Nevertheless, few studies to date have evaluated the association between ambient air pollution and AHR.^{17,25,26} Our own previous study showed an increase in the new diagnosis of AHR in children living closer to traffic roads.¹⁷ However, because distances from traffic roads do not coincide with PM₁₀ exposure, our previous and current studies have had slightly different findings. Additionally, PM_{2.5} exposure at birth was found to increase the incidence of AHR in high-risk schoolchildren in one report²⁶ but not in another prior study.²⁵ Our current study findings have indicated that early-life PM₁₀ exposure leads to AHR at an early school age.

Asymptomatic AHR often precedes the development of symptomatic asthma. A few studies have investigated the relationship between AHR in school-aged children and asthma development. A previous 12-year prospective follow-up study of children and adolescents (age range, 7-17 years) reported that the presence of AHR in childhood increased the risk of asthma development in adulthood.² Other studies have described that AHR at 10 years of age increased the prevalence³ and incidence⁴ of asthma in adolescents. One earlier study that investigated the effect of AHR in early school-aged children found that AHR at 6 years of age increased the incidence of new asthma diagnosis at age 22.¹ Because asthma is a complex set of pathophysiological processes rather than AHR alone,²⁶ AHR is not always coincident with asthma diagnosis or symptoms.²⁷ Several genetic or environmental factors may be associated with asthma development.⁶ It has been postulated that if children with AHR are exposed to an additional environmental trigger, asthma may develop in the near future.^{6,28} However, limited evidence is currently available on the precise environmental factors or times of exposure that increase the risk of a new diagnosis of asthma in children with asymptomatic AHR. Our current results do suggest that early-life PM₁₀ exposure in the second trimester may induce AHR at early school age, and this AHR may progress to asthma during the school period. However, we found that PM₁₀ exposure at 7 years did not interact with AHR for a new diagnosis of asthma at this age in our current series (Figure 3H).

Although the prenatal period has been previously considered to be a particularly susceptible period with regard to ambient air pollution exposure,¹² the critical period during pregnancy which such an exposure would have the greatest effect on asthma onset has not been well investigated. One study evaluated the effect of PM_{2.5} exposure during pregnancy on the development of asthma in pre-school children and found that 16-25 weeks of gestation is the

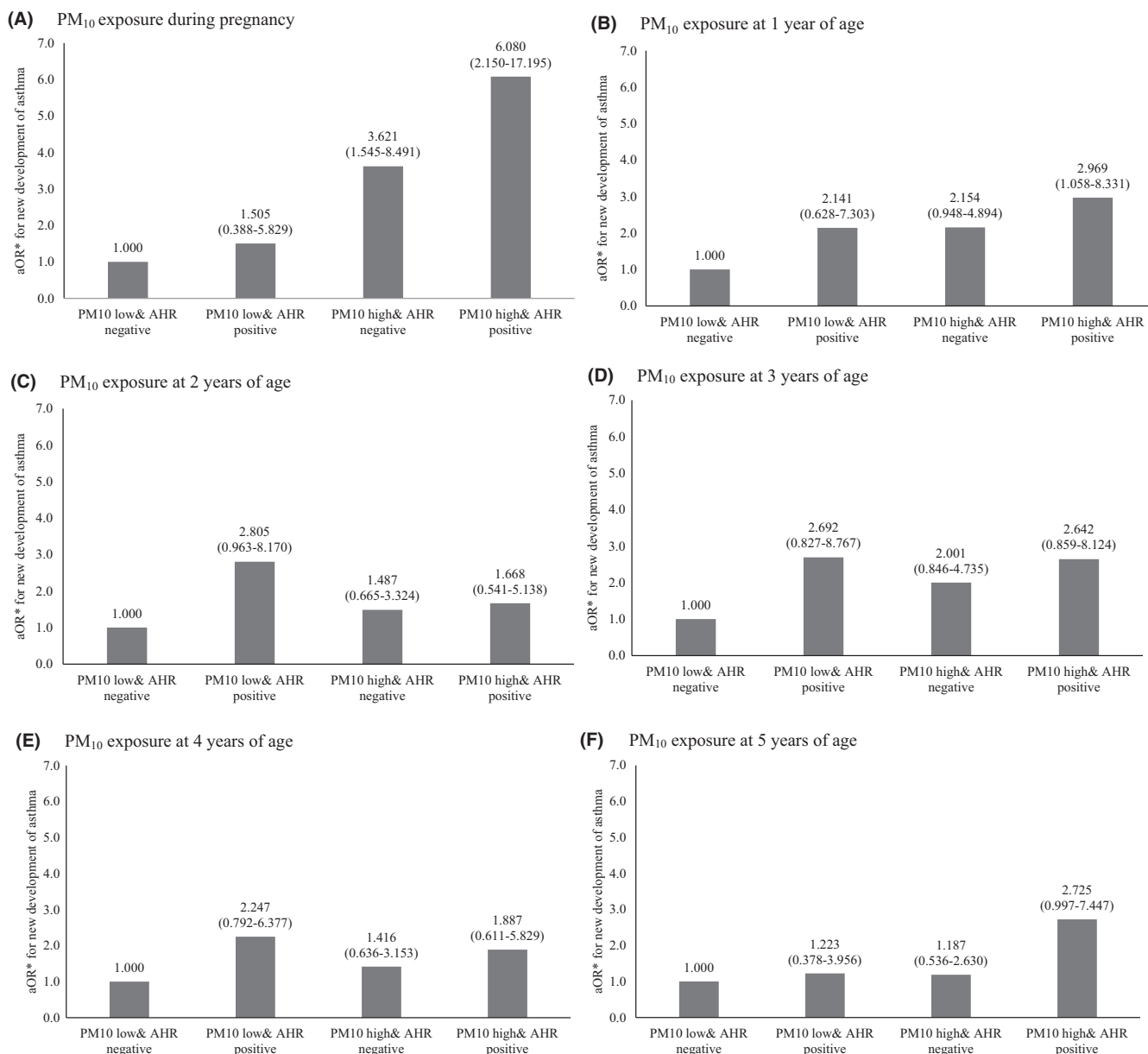


FIGURE 3 Combined effect of PM₁₀ exposure and AHR at 7 years on the new development of asthma at the 4-year follow-up. The risk of a new diagnosis of asthma by both higher PM₁₀ exposure and AHR at 7 years was highest for PM₁₀ exposure during pregnancy. *Adjusted for age, sex, body mass index, preterm birth, birthweight, maternal education level, exposure to environmental tobacco smoke, and parental history of allergic diseases

critical period.¹⁶ However, since asthma was assessed by questionnaire in subjects up to 6 years of age only in that study, there was a possibility that cases of wheezing respiratory illnesses other than asthma in preschool children were included in this study.

The children in our current study series with atopy showed a higher risk of AHR at age 7 following PM₁₀ exposure. Moreover, the risk of a new diagnosis of asthma as a result of PM₁₀ exposure was higher in children without atopy. Our findings in this regard must be interpreted with caution however because of the small number of cases in our series showing a new diagnosis of atopic asthma. Notably, however, other birth cohort studies have also reported higher risks of nonatopic asthma in relation to early-life PM exposure

compared with atopic asthma at 8 years of age.^{13,25} These previous results suggested that PM₁₀ exposure might affect the development of asthma even in non-atopic children. The most plausible mechanisms underlying these effects are likely to be related to reactive oxygen species, impaired lung development, and nonallergic inflammation.¹³

Our current study results indicate that the effects of PM₁₀ exposure different in boys and girls: The boys showed an association with AHR at age 7 and the girls with the new development of asthma at age 11. Previous studies have suggested that the effects of air pollution are stronger among boys during the preschool and early school periods and among girls in later childhood.^{29,30} It has been reported

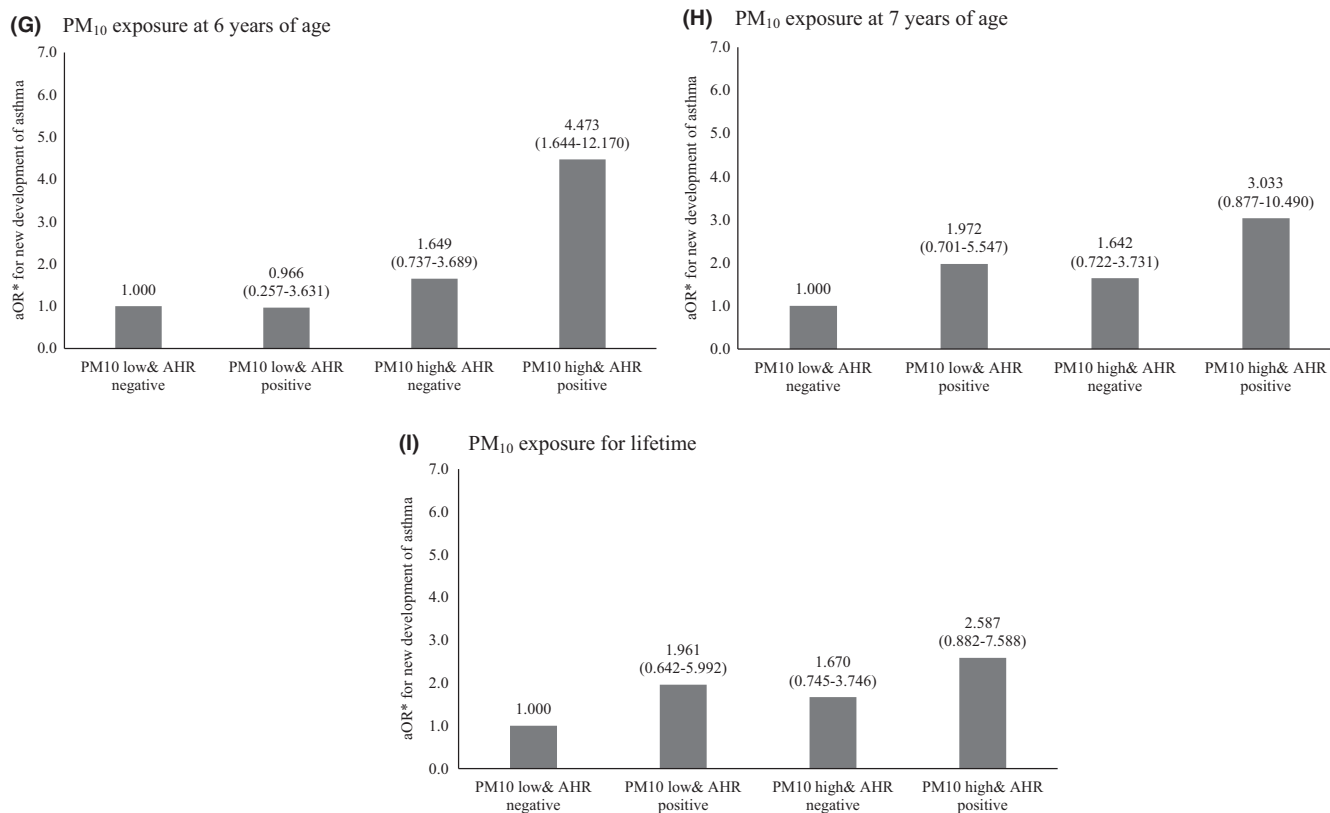


FIGURE 3 (Continued)

in this regard that different biological responses (eg, age, hormonal status, pubertal maturation, and body size) and exposure patterns (eg, activity patterns and co-exposures) may be associated with different responses between males and females.³⁰ Our present results are consistent with these previous findings and suggest that early-life PM₁₀ exposure can be considered as a risk factor for school-age asthma development in girls.

The mechanisms underlying the associations of PM₁₀ exposure during the second trimester of pregnancy with AHR/asthma in offspring are currently unknown. Prenatal lung development is categorized into five stages: embryonic (4–7 weeks), pseudoglandular (7–17 weeks), canalicular (17–26 weeks), saccular (27–36 weeks), and alveolar (36 weeks–2 years after birth).³¹ The effects of exposure to environmental pollutants on the respiratory system may be dependent on the stage of development. Asthma is associated with structural changes in the airways.³² Airway modeling during branching morphogenesis in the fetal lung is linked to the development of asthma.³² Genes that influence normal airway development and that are expressed during branching morphogenesis have been previously found to be associated with asthma.^{33,34} The second trimester of pregnancy coincides with the pseudoglandular and canalicular stage, which is the period of branching morphogenesis. Maternal and fetal placental circulation development starts during early pregnancy, but blood flow increases at the end of the first trimester.^{35,36} Hence, the direct effect of PM₁₀ exposure on fetal lung development via transplacental transport might not be significant during the first trimester.

Ambient air pollution induces oxidative stress.¹² The enzyme systems responsible for protecting the lung against oxidative stress are established during the mid- to late-gestational periods and continue to mature through to the early postnatal years. The immaturity of antioxidant activity increases the risk of oxidative stress and contributes to the development of asthma.³¹ Thus, the notion that PM₁₀ exposure during the second trimester might have more relevance to childhood asthma and AHR is biologically plausible.

This study had several limitations of note. The first of these was related to the exposure measurements. Because exposure modeling was used to estimate the PM₁₀ concentrations, some misclassification of its exposure was possible. It would not be feasible however to use individual and continuous direct pollutant monitoring for several years in a large general population. In addition, exposure modeling is widely used in epidemiologic studies to estimate exposure concentrations and we considered PM₁₀ to be a dichotomous measure for our current analyses. The association between PM₁₀ exposure and AHR/asthma may not be a natural linear-log relationship. Hence, continuous exposure analysis may not be suitable for assessing the PM₁₀ and AHR/asthma association. We also analyzed the association between continuous measures of PM₁₀ and AHR/asthma and obtained similar results. In addition, the mean concentrations of PM₁₀ were found to be correlated within the different exposure periods. It is difficult to extract the exposure effect on asthma/AHR with respect to each exposure period. Additionally, we did not evaluate the effect of other ambient/indoor pollutants, weather, other geologic factors, or diet. Further studies that incorporate these

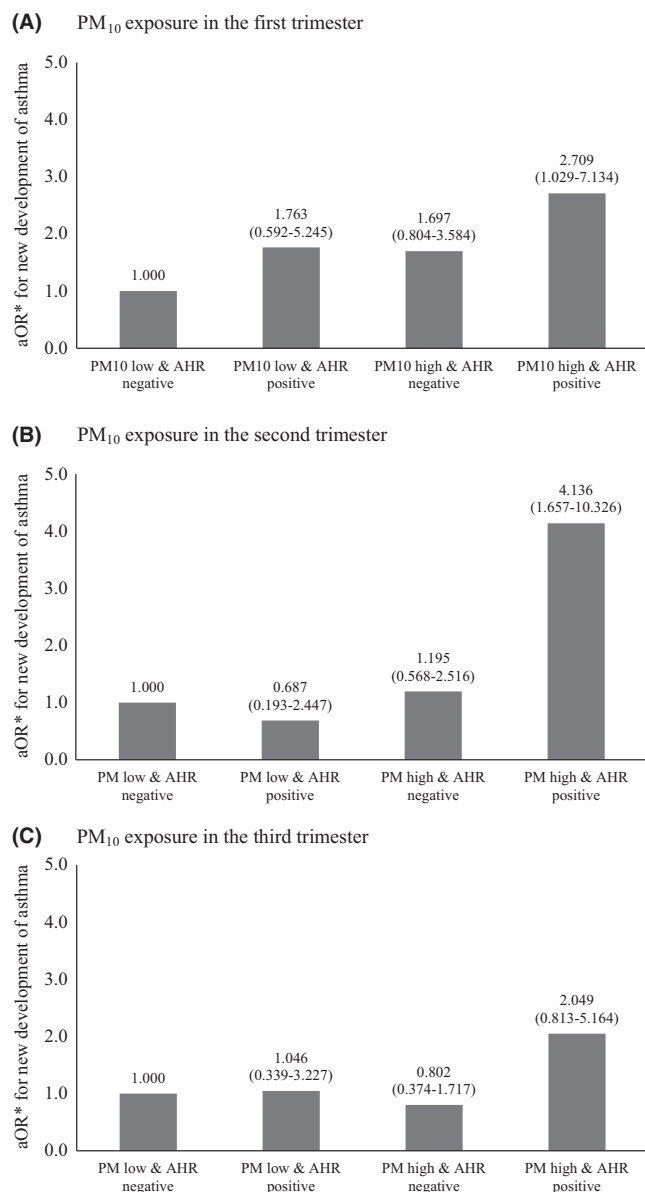


FIGURE 4 Combined effect of PM₁₀ exposure during pregnancy and AHR at 7 years on the new development of asthma at the 4-year follow-up. Higher PM₁₀ exposure during the second trimester of pregnancy interacts with an AHR at 7 years of age for the risk of a new diagnosis of asthma. *Adjusted for age, sex, body mass index, preterm birth, birthweight, maternal education level, exposure to environmental tobacco smoke, and parental history of allergic diseases

variables would provide a more precise assessment of the effect of air pollution on childhood asthma.

Another limitation of our current analysis was that AHR testing was not available for all of the children and some did not complete the follow-up. The methacholine challenge test was only performed in children for whom written consent was given. However, although the follow-up rate was relatively low, over 2000 children were followed and over 1000 children underwent a methacholine challenge test. AHR has not previously been investigated in a nationwide general population of this size, and this is therefore a considerable

strength of our current study. We tried to reduce any bias by adjusting for covariates that were different between children with and without AHR measurements or a follow-up status. A further limitation was that no personal histories of atopic dermatitis or allergic rhinitis were analyzed.

Notwithstanding the limitations of our present analyses, the longitudinal design of our assessment of a nationwide population of schoolchildren is a notable strength of our present study, even though there was a relatively short (4-year) follow-up. Our analysis was conducted in a general population of over 3500 schoolchildren nationwide. Previous studies have evaluated the association between ambient air pollution and AHR in high-risk children or children with asthma.^{25,26,37} Our current findings however can be considered to be nationally representative and thus have general applicability. In addition, asthma was defined in our present analysis using objective measures of AHR via a methacholine challenge test^{17,19} as well as by parental reporting of physician-diagnosed asthma using the well-validated ISAAC questionnaire.¹⁷⁻¹⁹ Hence, the frequency of outcome misclassification was reduced, and the reliability of our results was enhanced.

In conclusion, prenatal PM₁₀ exposure may induce AHR at 7 years of age and the second trimester of pregnancy is the most critical time for PM₁₀ exposure as it has the greatest positive impact on new diagnosis of asthma in school-aged children with AHR. A more strict monitoring and avoidance of exposure to PM, particularly during the second trimester of pregnancy, might considerably reduce the onset of future asthma and AHR development in schoolchildren.

AUTHOR CONTRIBUTION

Song-I Yang designed this study and wrote this manuscript. So-Yeon Lee, Hyo-Bin Kim, Hwan-Cheol Kim, Jong-Han Leem, Hyeon Jong Yang, Ju-Hee Seo, and Ho-Jang Kwon did the data collection. Hyeok Kwon did the data analysis. Hyun-Ju Cho, Jisun Yoon, Eun Lee, Young-Ho Jung, Young-Ho Kim, and Sungsu Jung searched literatures. Soo-Jong Hong designed this study and did the data interpretation. All authors reviewed and approved the final version of the report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Online Repository

Methacholine challenge test¹

Following a methacholine challenge, the forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured using a computerized spirometer (Microspiro HI-298; Chest Corporation, Tokyo, Japan) in accordance with the recommendations of the American Thoracic Society. Methacholine (Sigma Diagnostics, St. Louis, MO) solutions were prepared in buffered saline at different concentrations (0.625, 1.25, 2.5, 5, 1.5, and 25 mg/ml). A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, MD) was used to generate an aerosol from a DeVilbiss 646 nebulizer (DeVilbiss Health Care, Somerset, PA). Each subject inhaled five inspiratory capacity breaths of buffered saline solution and increasing concentrations of methacholine at 5-minute intervals. The procedure was terminated when the FEV₁ decreased by more than 20% of its post-saline value or when the highest methacholine (25 mg/ml) concentration was reached. The response to the methacholine challenge was expressed as the concentration that caused a decrease in the FEV₁ of 20% from baseline (PC₂₀).

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Table E1. Comparison of study population characteristics according to AHR measurements

	AHR measure (+) (n=1644)		AHR measure (-) (n=1926)		<i>p</i> value
	n	% or mean $\pm$ SD	n	% or mean $\pm$ SD	
Age (year)	1,644	7.3 $\pm$ 0.4	1,926	7.6 $\pm$ 0.6	<0.001
Male	853/1,644	51.9	996/1,926	51.7	0.92
Body mass index [†]	1,631		1,602		0.21
Normal	1,344	82.4	1,286	80.3	
Overweight	167	10.2	173	10.8	
Obesity	120	7.4	143	8.9	
Parental history of allergic disease	540/1,595	33.9	550/1,760	31.3	0.11
Maternal educational level ($\geq$ 16 years)	634/1,591	39.8	726/1,879	38.6	0.49
Prematurity [‡]	71/1,574	4.5	73/1,869	3.9	0.39
Low birth weight infants [§]	54/1,514	3.6	64/1,797	3.6	1.00
ETS exposure at first survey	459/1,591	28.8	572/1,884	30.4	0.33

[†]Overweight, 85th percentile $\leq$ BMI <95th percentile; obesity, BMI $\geq$ 95th percentile for children of the same age and sex.

[‡]Infants born before 37 weeks of gestation

[§]Birth weight < 2500 g

^{||}ETS: environmental tobacco smoke

Table E2. Comparison of study population characteristics according to follow-up status

	Follow-up (+) (n=2113)		Follow-up (-) (n=1457)		<i>p</i> value
	n	%	n	%	
Age (year)	2,076	7.46 ± 0.51	1457	7.54 ± 0.56	<0.001
Male	1,039/2,076	50.0	788/1,457	54.1	0.02
Body mass index [†]	1,998		1,203		0.02
Normal	1,602	80.2	1,003	83.4	
Overweight	214	10.7	123	10.2	
Obesity	182	9.1	77	6.4	
Parental history of allergic disease	826/2,058	40.1	253/1,263	20.0	<0.001
Maternal educational level (≥ 16 years)	765/2,013	38.0	587/1,425	41.2	0.06
Prematurity [‡]	78/1,998	3.9	64/1,417	4.5	0.38
Low birth weight infants [§]	72/1,902	3.8	44/1,376	3.2	0.37
ETS exposure at first survey	620/2,017	30.7	404/1,429	28.3	0.12

[†]Overweight; 85th percentile ≤ BMI < 95th percentile, obesity; BMI ≥ 95th percentile for children of the same age and sex

[‡] Infants born before 37 weeks of gestation

[§]Birth weight < 2500 g

^{||}ETS: environmental tobacco smoke

Table E3. Annual PM₁₀ exposure levels

	mean	SD	95% CI	
Pregnancy	58.29	13.10	57.89	58.69
1 yr	56.37	11.39	56.06	56.68
2 yr	57.27	11.00	56.97	57.57
3 yr	57.30	10.71	57.01	57.59
4 yr	56.19	10.79	55.91	56.48
5 yr	56.74	9.89	56.49	57.00
6 yr	56.64	8.78	56.42	56.86
7 yr	56.26	8.07	56.04	56.48
Lifetime	57.05	8.36	56.79	57.32

Table E4. Risk of airway hyperresponsiveness according to the PM₁₀ exposure level and period

		AHR (-)		AHR (+)		a OR*	95% CI		p value
Pregnancy	low	823	64.0%	193	53.9%				
	high	463	36.0%	165	46.1%	1.694	1.298	2.209	<0.001
	total	1286	100.0%	358	100.0%				
1 yr	low	739	57.5%	162	45.3%				
	high	547	42.5%	196	54.70%	1.750	1.343	2.282	<0.001
	total	1286	100.0%	358	100.0%				
2 yr	low	714	55.5%	162	45.3%				
	high	572	44.5%	196	54.7%	1.485	1.141	1.932	0.003
	total	1286	100.0%	358	100.0%				
3 yr	low	613	47.7%	147	41.1%				
	high	673	52.3%	211	58.9%	1.335	1.023	1.743	0.034
	total	1286	100.0%	358	100.0%				
4 yr	low	728	56.8%	172	48.0%				
	high	554	43.2%	186	52.0%	1.401	1.076	1.824	0.012
	total	1282	100.0%	358	100.0%				
5 yr	low	733	57.4%	189	52.9%				
	high	545	42.6%	168	47.1%	1.229	0.944	1.600	0.125
	total	1278	100.0%	357	100.0%				
6 yr	low	661	51.8%	176	49.3%				
	high	615	48.2%	181	50.7%	1.167	0.898	1.516	0.249
	total	1276	100.0%	357	100.0%				
7 yr	low	607	47.6%	191	53.5%				
	high	669	52.4%	166	46.5%	0.751	0.577	0.977	0.033

	total	1276	100.0%	357	100.0%				
Lifetime	low	733	57.4%	182	51.0%				
	high	543	42.6%	175	49.0%	1.364	1.047	1.778	0.022
	total	1276	100.0%	357	100.0%				

*Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E5. Risk of asthma diagnosis ever by the year of first survey according to PM₁₀ exposure level and period

		asthma diagnosis, ever (-)		asthma diagnosis, ever (+)		a OR [*]	95% CI		p value
Pregnancy	low	1574	50.8%	190	44.5%	1.000			
	high	1527	49.2%	237	55.5%	1.201	0.944	1.526	0.136
		3101	100.0%	427	100.0%				
1 yr	low	1560	50.3%	204	47.8%	1.000			
	high	1541	49.7%	223	52.2%	1.060	0.834	1.348	0.634
		3101	100.0%	427	100.0%				
2 yr	low	1513	48.8%	213	49.9%	1.000			
	high	1588	51.2%	214	50.1%	0.902	0.710	1.147	0.402
		3101	100.0%	427	100.0%				
3 yr	low	1541	49.7%	216	50.6%	1.000			
	high	1560	50.3%	211	49.4%	0.976	0.767	1.242	0.844
		3101	100.0%	427	100.0%				
4 yr	low	1542	49.8%	225	52.8%	1.000			
	high	1556	50.2%	201	47.2%	0.828	0.651	1.054	0.125
		3098	100.0%	426	100.0%				
5 yr	low	1526	49.3%	232	54.6%	1.000			
	high	1568	50.7%	193	45.4%	0.652	0.512	0.831	0.001
		3094	100.0%	425	100.0%				
6 yr	low	1530	49.5%	215	50.8%	1.000			
	high	1559	50.5%	208	49.2%	0.856	0.672	1.091	0.209
		3089	100.0%	423	100.0%				
7 yr	low	1514	49.0%	231	54.6%	1.000			
	high	1575	51.0%	192	45.4%	0.729	0.572	0.929	0.011
		3089	100.0%	423	100.0%				

Lifetime	low	1524	49.3%	229	54.1%	1.000			
	high	1565	50.7%	194	45.9%	0.699	0.548	0.891	0.004
		3089	100.0%	423	100.0%				

*Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E6. Risk of new development of AHR according to PM₁₀ exposure level and period

		new AHR (-)		new AHR (+)		a OR [*]	95% CI		p value
Pregnancy	low	461	62.4%	50	72.5%				
	high	278	37.6%	19	27.5%	0.649	0.344	1.226	0.183
		739	100.0%	69	100.0%				
1 yr	low	400	54.1%	43	62.3%				
	high	339	45.9%	26	37.7%	0.570	0.311	1.044	0.069
		739	100.0%	69	100.0%				
2 yr	low	384	52.0%	40	58.0%				
	high	355	48.0%	29	42.0%	0.724	0.405	1.294	0.276
		739	100.0%	69	100.0%				
3 yr	low	343	46.4%	26	37.7%				
	high	396	53.6%	43	62.3%	1.698	0.932	3.094	0.084
		739	100.0%	69	100.0%				
4 yr	low	410	55.6%	47	68.1%				
	high	327	44.4%	22	31.9%	0.493	0.263	0.925	0.027
		737	100.0%	69	100.0%				
5 yr	low	404	55.0%	43	62.3%				
	high	330	45.0%	26	37.7%	0.735	0.407	1.327	0.307
		734	100.0%	69	100.0%				
6 yr	low	387	52.9%	39	56.5%				
	high	345	47.1%	30	43.5%	0.778	0.436	1.389	0.396
		732	100.0%	69	100.0%				
7yr	low	354	48.4%	32	46.4%				
	high	378	51.6%	37	53.6%	1.233	0.694	2.192	0.475
		732	100.0%	69	100.0%				

Lifetime	low	404	55.2%	40	58.0%				
	high	328	44.8%	29	42.0%	0.847	0.468	1.534	0.585
		732	100.0%	69	100.0%				

*Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E7. Risk of new development of asthma according to PM₁₀ exposure level and period

		New asthma diagnosis (-)		New asthma diagnosis (+)		a OR*	95% CI		p value
Pregnancy	low	919	53.4%	31	35.6%				
	high	801	46.6%	56	64.4%	2.056	1.240	3.409	0.005
	total	1720	100.0%	87	100.0%				
1 yr	low	876	50.9%	34	39.1%				
	high	844	49.1%	53	60.9%	1.529	0.933	2.506	0.092
	total	1720	100.0%	87	100.0%				
2 yr	low	827	48.1%	29	33.3%				
	high	893	51.9%	58	66.7%	1.488	0.902	2.454	0.120
	total	1720	100.0%	87	100.0%				
3 yr	low	831	48.3%	30	34.5%				
	high	889	51.7%	57	65.5%	1.589	0.959	2.633	.072
	total	1720	100.0%	87	100.0%				
4 yr	low	850	49.5%	33	37.9%				
	high	868	50.5%	54	62.1%	1.272	0.777	2.081	0.338
	total	1718	100.0%	87	100.0%				
5 yr	low	821	47.9%	31	35.6%				
	high	894	52.1%	56	64.4%	1.409	0.851	2.333	0.183
	total	1715	100.0%	87	100.0%				
6 yr	low	898	52.5%	41	47.1%				
	high	813	47.5%	46	52.9%	1.233	0.759	2.004	0.398
	total	1711	100.0%	87	100.0%				
7 yr	low	856	50.0%	43	49.4%				
	high	855	50.0%	44	50.6%	1.093	0.675	1.771	0.716
	total	1711	100.0%	87	100.0%				

Lifetime	low	838	49.0%	34	39.1%				
	high	873	51.0%	53	60.9%	1.475	0.890	2.445	0.131
	total	1711	100.0%	87	100.0%				

*Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E8. Combined effect of PM₁₀ exposure and AHR at 7 years of age on the new development of asthma at the four-year follow-up

Pregnancy		a OR*	95% CI		<i>p</i> value	interaction <i>P</i>
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	1.505	0.388	5.829	0.554	
PM ₁₀ high	AHR negative	3.621	1.545	8.491	0.003	
PM ₁₀ high	AHR positive	6.080	2.150	17.195	0.001	0.897
1 yr						
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	2.141	0.628	7.303	0.224	
PM ₁₀ high	AHR negative	2.154	0.948	4.894	0.067	
PM ₁₀ high	AHR positive	2.969	1.058	8.331	0.039	0.581
2 yr						
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	2.805	0.963	8.170	0.059	
PM ₁₀ high	AHR negative	1.487	0.665	3.324	0.334	
PM ₁₀ high	AHR positive	1.668	0.541	5.138	0.373	0.240
3 yr						
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	2.692	0.827	8.767	0.100	
PM ₁₀ high	AHR negative	2.001	0.846	4.735	0.114	
PM ₁₀ high	AHR positive	2.642	0.859	8.124	0.090	0.368
4 yr						
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	2.247	0.792	6.377	0.128	
PM ₁₀ high	AHR negative	1.416	0.636	3.153	0.394	
PM ₁₀ high	AHR positive	1.887	0.611	5.829	0.270	0.500

5 yr						
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	1.223	0.378	3.956	0.737	
PM ₁₀ high	AHR negative	1.187	0.536	2.630	0.673	
PM ₁₀ high	AHR positive	2.725	0.997	7.447	0.051	0.423
6 yr						
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	0.966	0.257	3.631	0.960	
PM ₁₀ high	AHR negative	1.649	0.737	3.689	0.223	
PM ₁₀ high	AHR positive	4.473	1.644	12.170	0.003	0.218
7 yr						
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	1.972	0.701	5.547	0.198	
PM ₁₀ high	AHR negative	1.642	0.722	3.731	0.237	
PM ₁₀ high	AHR positive	3.033	0.877	10.490	0.080	0.935
Lifetime						
PM ₁₀ low	AHR negative	1.000				
PM ₁₀ low	AHR positive	1.961	0.642	5.992	0.237	
PM ₁₀ high	AHR negative	1.670	0.745	3.746	0.213	
PM ₁₀ high	AHR positive	2.587	0.882	7.588	0.083	0.984

*Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E9. Combined effect of PM₁₀ exposure during pregnancy and AHR at 7 years of age on the new development of asthma at the four- year follow-up

		a OR [*]	95% CI		<i>p</i> value	interaction <i>p</i>
1 st trimester						
PM ₁₀ low	AHR negative	1.000				0.390
PM ₁₀ low	AHR positive	1.763	0.592	5.245	0.308	
PM ₁₀ high	AHR negative	1.697	0.804	3.584	0.165	
PM ₁₀ high	AHR positive	2.709	1.029	7.134	0.044	
2 nd trimester						
PM ₁₀ low	AHR negative	1.000				0.001
PM ₁₀ low	AHR positive	0.687	0.193	2.447	0.562	
PM ₁₀ high	AHR negative	1.195	0.568	2.516	0.639	
PM ₁₀ high	AHR positive	4.136	1.657	10.326	0.002	
3 rd trimester						
PM ₁₀ low	AHR negative	1.000				0.210
PM ₁₀ low	AHR positive	1.046	0.339	3.227	0.938	
PM ₁₀ high	AHR negative	0.802	0.374	1.717	0.569	
PM ₁₀ high	AHR positive	2.049	0.813	5.164	0.128	

*Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E10. Effect of PM₁₀ exposure on the risk of respiratory outcomes according to the presence of atopy

Atopy* (-)					Atopy* (+)			
AHR [#] by the year of first survey								
	a OR [‡]	95% CI		p value	a OR [‡]	95% CI		p value
first trimester	1.173	0.765	1.799	0.465	1.192	0.756	1.879	0.450
second trimester	0.731	0.467	1.145	0.172	0.937	0.585	1.501	0.787
third trimester	0.989	0.637	1.536	0.961	1.012	0.642	1.596	0.959
pregnancy	1.028	0.601	1.759	0.920	1.928	1.157	3.212	0.012
1yr	1.238	0.748	2.051	0.407	2.951	1.769	4.924	0.000
2yr	1.055	0.641	1.736	0.834	2.043	1.239	3.370	0.005
3yr	0.905	0.551	1.487	0.694	1.224	0.744	2.015	0.427
4yr	0.991	0.584	1.681	0.972	1.437	0.865	2.387	0.162
5yr	0.719	0.429	1.204	0.210	1.189	0.725	1.951	0.493
6yr	0.775	0.463	1.298	0.333	1.286	0.789	2.095	0.312
7yr	1.060	0.640	1.758	0.820	0.633	0.389	1.031	0.066
asthma diagnosis ever by the year of first survey								
	a OR [‡]	95% CI		p value	a OR [‡]	95% CI		p value
first trimester	0.718	0.392	1.315	0.284	1.059	0.605	1.853	0.842
second trimester	0.970	0.536	1.758	0.921	0.967	0.543	1.722	0.909
third trimester	1.126	0.622	2.038	0.694	0.784	0.442	1.388	0.403
pregnancy	0.841	0.426	1.658	0.616	1.012	0.541	1.893	0.971
1yr	1.010	0.542	1.882	0.974	1.004	0.544	1.850	0.991
2yr	0.983	0.532	1.818	0.957	0.882	0.476	1.635	0.691
3yr	1.948	1.038	3.656	0.038	0.790	0.434	1.437	0.439
4yr	0.962	0.496	1.865	0.909	0.864	0.460	1.622	0.648
5yr	0.781	0.415	1.468	0.442	0.536	0.286	1.004	0.051
6yr	0.701	0.370	1.328	0.276	0.787	0.434	1.425	0.429
7yr	0.972	0.530	1.780	0.926	0.710	0.394	1.281	0.255
new development of AHR [#]								
	a OR [‡]	95% CI		p value	a OR [‡]	95% CI		p value
first trimester	1.532	0.688	3.412	0.297	0.677	0.219	2.094	0.498
second trimester	0.723	0.325	1.609	0.427	1.276	0.412	3.952	0.673
third trimester	2.024	0.891	4.598	0.092	0.503	0.137	1.850	0.301
pregnancy	1.019	0.388	2.678	0.969	1.346	0.349	5.186	0.666
1yr	0.601	0.231	1.565	0.297	0.684	0.193	2.427	0.557
2yr	1.197	0.490	2.921	0.693	0.997	0.295	3.369	0.996
3yr	2.441	0.962	6.189	0.060	1.564	0.479	5.104	0.459
4yr	0.921	0.351	2.418	0.867	0.318	0.071	1.434	0.136
5yr	0.594	0.228	1.544	0.285	0.980	0.271	3.552	0.976

6yr	0.602	0.230	1.577	0.301	0.779	0.224	2.704	0.694
7yr	0.869	0.368	2.053	0.749	2.526	0.661	9.650	0.175
new development of asthma								
	a OR [‡]	95% CI		p value	a OR [‡]	95% CI		p value
first trimester	6.901	1.882	25.298	0.004	1.629	0.316	8.383	0.559
second trimester	1.269	0.449	3.591	0.653	10.529	0.966	114.792	0.053
third trimester	2.020	0.668	6.107	0.213	0.282	0.046	1.719	0.170
pregnancy	5.841	1.725	19.783	0.005	4.260	0.704	25.780	0.115
1yr	2.502	0.798	7.851	0.116	5.554	0.906	34.058	0.064
2yr	2.157	0.671	6.937	0.197	2.466	0.475	12.800	0.283
3yr	1.863	0.593	5.853	0.287	1.083	0.213	5.517	0.924
4yr	1.658	0.526	5.225	0.388	2.648	0.477	14.693	0.265
5yr	1.764	0.571	5.454	0.324	1.305	0.244	6.975	0.756
6yr	2.276	0.709	7.301	0.167	5.243	0.741	37.074	0.097
7yr	1.792	0.571	5.627	0.318	0.735	0.152	3.569	0.703

*Presence of one or more positive reactions via the skin prick test

#AHR, airway hyperresponsiveness

‡Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E11. Combined effect of PM₁₀ exposure and AHR at 7 years of age on the new diagnosis of asthma after the 4-year follow-up according to the presence of atopy

			Atopy* (-)				Atopy* (+)			
			a OR [‡]	95% CI		p value	a OR [‡]	95% CI		p value
first trimester	PM ₁₀ low	AHR [#] negative	1.000				1.000			
	PM ₁₀ low	AHR positive	4.425	0.391	50.068	0.230	0.000	0.000	.	0.998
	PM ₁₀ high	AHR negative	8.755	1.989	38.550	0.004	0.678	0.092	4.985	0.703
	PM ₁₀ high	AHR positive	17.690	2.156	145.119	0.007	1.943	0.292	12.905	0.492
second trimester	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	2.229	0.384	12.939	0.372	0.000	0.000	.	0.998
	PM ₁₀ high	AHR negative	1.386	0.440	4.367	0.578	2.977	0.232	38.218	0.402
	PM ₁₀ high	AHR positive	3.967	0.406	38.806	0.236	12.839	0.935	176.231	0.056
third trimester	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	3.010	0.514	17.615	0.221	0.250	0.022	2.880	0.266
	PM ₁₀ high	AHR negative	2.311	0.678	7.877	0.180	0.000	0.000	.	0.997
	PM ₁₀ high	AHR positive	3.900	0.399	38.124	0.242	0.641	0.085	4.846	0.666
pregnancy	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	5.316	0.725	38.995	0.100	0.000	0.000	.	0.998
	PM ₁₀ high	AHR negative	8.399	1.992	35.415	0.004	1.646	0.190	14.241	0.651
	PM ₁₀ high	AHR positive	31.316	1.929	508.348	0.015	3.738	0.506	27.595	0.196
1yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	4.585	0.656	32.036	0.125	3.895	0.164	92.680	0.400
	PM ₁₀ high	AHR negative	3.232	0.879	11.883	0.077	22.843	1.322	394.610	0.031
	PM ₁₀ high	AHR positive	5.905	0.525	66.374	0.150	4.761	0.293	77.257	0.272
2yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	11.999	1.892	76.112	0.008	1.099	0.076	15.789	0.945
	PM ₁₀ high	AHR negative	4.354	1.044	18.163	0.044	3.493	0.378	32.243	0.270
	PM ₁₀ high	AHR positive	0.000	0.000	.	0.999	2.183	0.231	20.647	0.496
3yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	9.514	1.511	59.891	0.016	0.695	0.050	9.742	0.787
	PM ₁₀ high	AHR negative	3.794	0.917	15.689	0.066	0.946	0.119	7.516	0.958
	PM ₁₀ high	AHR positive	0.000	0.000	.	0.999	1.045	0.105	10.422	0.970
4yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	5.423	1.066	27.577	0.042	0.703	0.052	9.497	0.791
	PM ₁₀ high	AHR negative	2.528	0.709	9.005	0.153	2.229	0.260	19.078	0.464

	PM ₁₀ high	AHR positive	0.000	0.000	.	0.999	2.654	0.265	26.551	0.406
5yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	6.346	1.167	34.496	0.032	0.000	0.000	.	0.998
	PM ₁₀ high	AHR negative	3.081	0.824	11.524	0.095	0.211	0.018	2.503	0.217
	PM ₁₀ high	AHR positive	0.000	0.000	.	0.999	1.876	0.223	15.773	0.563
6yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	4.041	0.608	26.851	0.148	0	0	.	0.998
	PM ₁₀ high	AHR negative	3.098	0.81	11.853	0.099	1.438	0.163	12.674	0.744
	PM ₁₀ high	AHR positive	7.926	0.63	99.67	0.109	5.944	0.583	60.596	0.132
7yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	17.124	2.13	137.633	0.008	0.216	0.015	3.181	0.264
	PM ₁₀ high	AHR negative	4.884	0.985	24.202	0.052	0.279	0.034	2.318	0.238
	PM ₁₀ high	AHR positive	0.000	0.000	.	0.999	0.814	0.088	7.545	0.856

*Presence of one or more positive reactions via the skin prick test

#AHR, airway hyperresponsiveness

‡Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E12. Effect of PM₁₀ exposure on the risk of respiratory outcomes according to sex

Male					Female			
AHR*by the year of first survey								
	a OR [#]	95% CI		p value	a OR [#]	95% CI		p value
first trimester	1.351	0.930	1.961	0.114	1.736	1.179	2.555	0.005
second trimester	1.165	0.798	1.700	0.428	0.997	0.672	1.479	0.988
third trimester	1.400	0.952	2.060	0.087	0.972	0.660	1.433	0.887
pregnancy	2.057	1.414	2.991	0.000	1.288	0.872	1.903	0.203
1yr	2.037	1.401	2.964	0.000	1.462	0.994	2.151	0.054
2yr	1.800	1.240	2.615	0.002	1.173	0.801	1.719	0.413
3yr	1.358	0.928	1.988	0.115	1.244	0.850	1.819	0.261
4yr	1.761	1.213	2.558	0.003	1.039	0.708	1.526	0.845
5yr	1.385	0.956	2.006	0.085	1.042	0.709	1.530	0.835
6yr	1.321	0.912	1.913	0.141	0.994	0.680	1.452	0.974
7yr	0.810	0.560	1.171	0.263	0.691	0.472	1.012	0.058
Asthma diagnosis ever by the year of first survey								
	a OR [#]	95% CI		p value	a OR [#]	95% CI		p value
first trimester	1.029	0.751	1.409	0.858	0.710	0.485	1.041	0.079
second trimester	0.971	0.700	1.347	0.861	1.018	0.694	1.495	0.926
third trimester	1.031	0.748	1.421	0.853	0.843	0.576	1.233	0.379
pregnancy	1.258	0.918	1.723	0.153	1.088	0.748	1.582	0.660
1yr	1.145	0.836	1.569	0.397	0.933	0.641	1.360	0.719
2yr	0.950	0.694	1.300	0.748	0.878	0.601	1.281	0.498
3yr	1.166	0.848	1.603	0.344	0.759	0.519	1.109	0.154
4yr	0.838	0.612	1.146	0.268	0.828	0.566	1.211	0.329
5yr	0.600	0.437	0.823	0.002	0.739	0.506	1.081	0.119
6yr	0.916	0.669	1.256	0.587	0.790	0.538	1.158	0.227
7yr	0.762	0.556	1.043	0.090	0.705	0.480	1.037	0.076
New development of AHR*								

	a OR[#]	95% CI		p value	a OR[#]	95% CI		p value
first trimester	1.376	0.616	3.073	0.436	1.337	0.534	3.346	0.536
second trimester	1.031	0.460	2.311	0.940	0.786	0.309	2.000	0.613
third trimester	0.837	0.356	1.966	0.682	1.615	0.641	4.067	0.309
pregnancy	0.629	0.267	1.481	0.289	0.647	0.224	1.863	0.419
1yr	0.411	0.174	0.971	0.043	0.607	0.231	1.597	0.312
2yr	0.496	0.218	1.131	0.096	0.904	0.367	2.229	0.826
3yr	1.231	0.547	2.769	0.616	2.227	0.863	5.746	0.098
4yr	0.384	0.157	0.942	0.037	0.531	0.197	1.433	0.211
5yr	0.677	0.298	1.542	0.353	0.820	0.326	2.060	0.673
6yr	0.831	0.377	1.833	0.646	0.713	0.284	1.789	0.472
7yr	1.290	0.580	2.870	0.532	1.244	0.511	3.028	0.630
New development of asthma								
	a OR[#]	95% CI		p value	a OR[#]	95% CI		p value
first trimester	1.959	0.996	3.851	0.051	1.537	0.714	3.312	0.272
second trimester	1.178	0.609	2.280	0.627	2.419	1.044	5.605	0.039
third trimester	0.635	0.323	1.248	0.188	1.991	0.897	4.418	0.090
pregnancy	2.237	1.135	4.409	0.020	2.105	0.955	4.640	0.065
1yr	1.487	0.777	2.844	0.231	1.795	0.808	3.985	0.151
2yr	1.201	0.630	2.290	0.577	2.196	0.946	5.099	0.067
3yr	1.481	0.766	2.864	0.243	1.912	0.846	4.319	0.119
4yr	0.791	0.418	1.496	0.470	2.897	1.204	6.971	0.018
5yr	0.917	0.480	1.751	0.793	2.931	1.222	7.028	0.016
6yr	0.928	0.490	1.758	0.819	1.994	0.903	4.404	0.088
7yr	0.708	0.373	1.343	0.290	2.074	0.938	4.583	0.071

*AHR, airway hyperresponsiveness

[#]Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases

Table E13. Combined effect of PM₁₀ exposure and AHR at 7 years of age on the new diagnosis of asthma after the 4-year follow-up according to sex

			Male				Female			
			a OR*	95% CI		p value	a OR*	95% CI		p value
first trimester	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	2.523	0.510	12.476	0.256	0.731	0.083	6.435	0.777
	PM ₁₀ high	AHR negative	1.751	0.591	5.188	0.312	1.215	0.348	4.245	0.760
	PM ₁₀ high	AHR positive	1.970	0.449	8.646	0.369	3.587	0.904	14.235	0.069
second trimester	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	0.849	0.160	4.492	0.847	0.741	0.078	7.028	0.794
	PM ₁₀ high	AHR negative	0.981	0.336	2.863	0.971	2.134	0.583	7.816	0.252
	PM ₁₀ high	AHR positive	2.803	0.719	10.930	0.138	7.989	1.692	37.711	0.009
third trimester	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	0.960	0.193	4.766	0.960	1.827	0.316	10.582	0.501
	PM ₁₀ high	AHR negative	0.344	0.099	1.199	0.094	1.880	0.526	6.714	0.331
	PM ₁₀ high	AHR positive	1.188	0.292	4.832	0.810	3.686	0.734	18.496	0.113
pregnancy	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	1.645	0.305	8.884	0.563	1.830	0.156	21.437	0.630
	PM ₁₀ high	AHR negative	2.517	0.828	7.655	0.104	8.537	1.757	41.471	0.008
	PM ₁₀ high	AHR positive	3.172	0.780	12.895	0.107	19.593	3.176	120.876	0.001
1yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	1.689	0.305	9.363	0.549	4.336	0.573	32.825	0.156
	PM ₁₀ high	AHR negative	1.266	0.438	3.661	0.664	6.856	1.409	33.353	0.017
	PM ₁₀ high	AHR positive	1.865	0.485	7.173	0.364	8.989	1.355	59.644	0.023
2yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	1.961	0.449	8.558	0.370	6.699	1.052	42.677	0.044
	PM ₁₀ high	AHR negative	0.791	0.274	2.283	0.664	4.921	1.018	23.789	0.047
	PM ₁₀ high	AHR positive	1.139	0.260	4.988	0.863	4.167	0.538	32.244	0.172
3yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	1.712	0.299	9.809	0.546	5.136	0.811	32.531	0.082
	PM ₁₀ high	AHR negative	1.385	0.465	4.120	0.559	4.082	0.859	19.394	0.077
	PM ₁₀ high	AHR positive	2.090	0.514	8.493	0.303	4.530	0.590	34.772	0.146
4yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	1.639	0.385	6.978	0.503	5.552	0.875	35.226	0.069
	PM ₁₀ high	AHR negative	0.619	0.203	1.887	0.399	5.474	1.146	26.141	0.033

	PM ₁₀ high	AHR positive	1.098	0.246	4.906	0.903	5.710	0.745	43.755	0.094
5yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	1.002	0.195	5.165	0.998	2.122	0.335	13.453	0.425
	PM ₁₀ high	AHR negative	0.605	0.201	1.821	0.371	3.241	0.835	12.582	0.089
	PM ₁₀ high	AHR positive	1.600	0.425	6.023	0.487	7.081	1.276	39.286	0.025
6yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	1.155	0.220	6.064	0.865	0.980	0.097	9.895	0.986
	PM ₁₀ high	AHR negative	1.233	0.427	3.556	0.699	3.051	0.784	11.872	0.108
	PM ₁₀ high	AHR positive	2.551	0.635	10.250	0.187	10.327	2.016	52.889	0.005
7yr	PM ₁₀ low	AHR negative	1.000				1.000			
	PM ₁₀ low	AHR positive	1.742	0.423	7.170	0.442	2.777	0.523	14.737	0.230
	PM ₁₀ high	AHR negative	1.473	0.504	4.302	0.479	2.409	0.617	9.409	0.206
	PM ₁₀ high	AHR positive	2.437	0.435	13.639	0.311	4.028	0.619	26.199	0.145

*Adjusted for age, sex, body mass index, preterm birth, birth weight, maternal education level, exposure to environmental tobacco smoke and parental history of allergic diseases