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Prenatal particulate matter exposure with skin barrier dysfunction affects offspring's atopic dermatitis: COCOA study

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Running title: Effect of prenatal PM exposure and skin barrier dysfunction on AD

Conflicts of interest

The authors declare no conflicts of interest in relation to this study.

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47 Statement of Contribution

48 Lee E, Hong SJ: designed and wrote the manuscript and performed the analyses. Lee SY,
49 Kim HC, Choi KY, Kim HB, Park MJ, Rhee ES, Yoon JS, Cho HJ, Jung SS Ahn KM, Kim
50 KW, Shin YH, and Suh DI participated in the collection, analysis, and interpretation of the
51 data. Hong SJ supervised the execution of the study.

52 **Clinical Implications**

53 Prenatal particulate matter (PM) exposure in the first trimester increases the risks of atopic
54 dermatitis (AD) in offspring. When combined with early life skin barrier dysfunction, PM
55 exposure during the first trimester may affect early-onset persistent AD phenotype.

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To the editor

The effects of ambient air pollution on atopic dermatitis (AD) development may be different according to the exposure timing, exposure levels, and types of ambient pollutants.¹ Considering that early life is a critical time for the determination of immune and structural development,² exposure to air pollution, especially in the prenatal period, might affect the development of AD. Skin barrier dysfunction is a key characteristic of AD,³ and air pollution exposure during specific periods in pregnancy might modify the effect of skin barrier dysfunction on AD (Figure E1 available in this article's Online Repository at www.jaci-inpractice.org). However, there are no previous studies on the combined effects of prenatal exposure to air pollution and skin barrier dysfunction on AD.

We investigated the effects of prenatal exposure to outdoor particulate matter (PM) with a diameter of less than 10 μg (PM_{10}) and less than 2.5 μg ($\text{PM}_{2.5}$) during the three trimesters on AD. Furthermore, we elucidated the combined effect of exposure to prenatal PM during specific trimesters and skin barrier dysfunction on AD and its phenotypes.

From the prospective Cohort for Childhood Origin of Asthma and Allergic Diseases (COCOA) birth cohort study,⁴ 468 infants with measurements of prenatal outdoor $\text{PM}_{10}/\text{PM}_{2.5}$ and trans-epidermal water loss (TEWL) levels at age 1 year were included (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The COCOA study enrolled pregnant women after 26 weeks of gestation with a mean gestational age of 35.0 weeks (standard deviation, 3.4 weeks) in Seoul.⁴ Pediatric allergists evaluated AD using the criteria of Hanifin and Rajka with SCORing Atopic Dermatitis (SCORAD) score.^{3,4} AD phenotypes were classified into 4 categories according to onset age and persistence of AD:

never, early transient, late onset, and early onset persistent.⁵ TEWL levels were measured at age 1 year. Concentrations of outdoor PM₁₀ and PM_{2.5} from pregnancy to 1 year of life at residential addresses were estimated weekly using land use regression models.⁶ This study was approved by the institutional board at Asan Medical Center and written consent was obtained from all parents.

When the outdoor PM₁₀/PM_{2.5} levels were divided into tertiles, the highest tertile of outdoor PM₁₀/PM_{2.5} exposure in the first trimester was more significantly associated with AD at age 1 year (adjusted odds ratio [aOR] 4.00, 95% confidence interval [CI] 1.43-11.23; aOR 2.19, 95% CI 1.43-3.62, respectively), compared to the lowest tertile of outdoor PM₁₀/PM_{2.5} levels (Figure 1, A). However, during the second and third trimesters, there was no significant association between the highest tertile of PM₁₀/PM_{2.5} exposure and AD at age 1 year, compared to the lowest tertile of PM₁₀/PM_{2.5} exposure. Exposure to PM₁₀/PM_{2.5} in the first trimester was positively related to the predicted probability of AD in both infants with low and high TEWL levels (Figure 2).

TEWL levels were dichotomized into low or high according to its mean (14.74 g/m²h). High TEWL levels were significantly associated with AD at age 1 year (aOR, 1.84; 95% CI, 1.09-3.10). Infants exposed to higher levels of PM₁₀ during the first trimester had a significantly higher risk of AD when their TEWL levels were high (aOR, 3.68; 95% CI, 1.01-13.46, Figure 1, B). A higher level of outdoor PM₁₀ exposure in the third trimester increased AD risk at age 1 year without significant interaction with higher TEWL levels. Infants exposed to higher levels of PM_{2.5} during the first trimester had a significantly higher risk of AD at age 1 year when their TEWL levels were high (aOR, 3.66; 95% CI, 1.10-12.19, interaction $P = .049$). Outdoor PM₁₀/PM_{2.5} exposure levels, during the first year of life alone and in combination

with skin barrier dysfunction, were not associated with the development of AD at age 1 year (data not shown). Exposure to high levels of outdoor PM₁₀/PM_{2.5} during the first trimester in infants with high TEWL was significantly associated with early-onset persistent AD (aOR 3.37, 95% CI 1.17-9.69; aOR 4.27, 95% CI, 1.58-11.54, respectively; Figure 1, C).

The levels of total serum IgE at birth showed an increasing trend according to outdoor PM₁₀/PM_{2.5} levels during the first trimester (Figure E2 available in this article's Online Repository at www.jaci-inpractice.org). Total serum IgE levels at age 1 year showed an increasing trend according to the combination of PM₁₀/PM_{2.5} levels during the first trimester and TEWL levels (Figure E3 available in this article's Online Repository at www.jaci-inpractice.org). SCORAD scores at age 3 years were highest in infants with high TEWL levels at age 1 year who were exposed to higher levels of PM₁₀/PM_{2.5} during the first trimester (Figure E4 available in this article's Online Repository at www.jaci-inpractice.org).

The association between prenatal exposure to outdoor PM and AD in early life might be partially due to changes in expression of pro-inflammatory cytokines and skin disease-related genes.³ Prenatal exposure to PM can induce epigenetic changes in fundamental DNA repair genes in the placenta,¹ which alters fetal and neonatal DNA repair capacity. Exposure to PM, even during short-term, can cause oxidative stress in the fetus through direct trans-placental transmission of oxidative stressors or their derivatives, leading to cellular damage and epigenetic changes.⁷ Increases in maternal oxidative stress during pregnancy might affect fetal immune development associated with AD.⁸ The effect of environmental factors on skin development and the associated immune system can be prominent in the first trimester, because the main immune cells in the skin, including Langerhans cells and dendritic cells, arise in the first trimester in the blood and mucosa.⁹ Allergic inflammation, as represented by

higher total serum IgE levels in early life, may be one of the underlying mechanisms that partially contributes to such associations (Figure E5 available in this article's Online Repository at www.jaci-inpractice.org).

In conclusion, prenatal exposure to higher levels of $PM_{10}/PM_{2.5}$ during the first trimester in itself and in combination with skin barrier dysfunction in early life increases AD risk at age 1 year. Exposure to higher levels of $PM_{10}/PM_{2.5}$ during the first trimester in infants with skin barrier dysfunction was associated with early-onset persistent AD and higher AD severity at age 3 years. These findings suggest that avoidance of air pollution, especially in the early gestational period, and enhancement of skin barrier in early life might be helpful in preventing the development or persistence of AD in infants.

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Figure legends

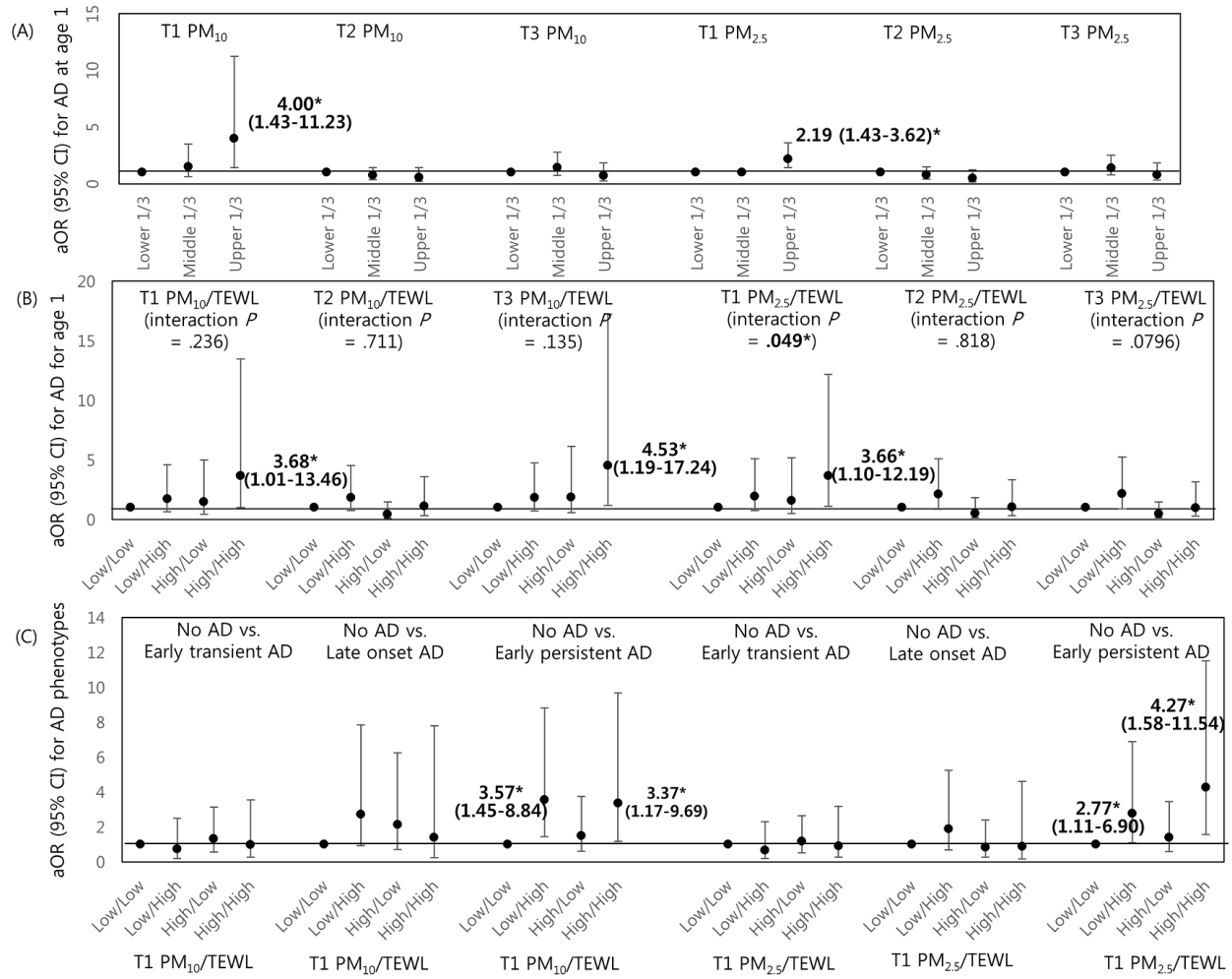
FIGURE 1. (A) Adjusted odds ratios for atopic dermatitis (AD) at age 1 in association with outdoor particulate matter (PM) levels during gestation. (B) The combined effect of outdoor $PM_{10}/PM_{2.5}$ exposure during the prenatal period and TEWL levels on AD at age 1. (C) Adjusted odds ratios for AD phenotypes in association with the combination of $PM_{10}/PM_{2.5}$ levels during the first trimester and TEWL levels at age 1.

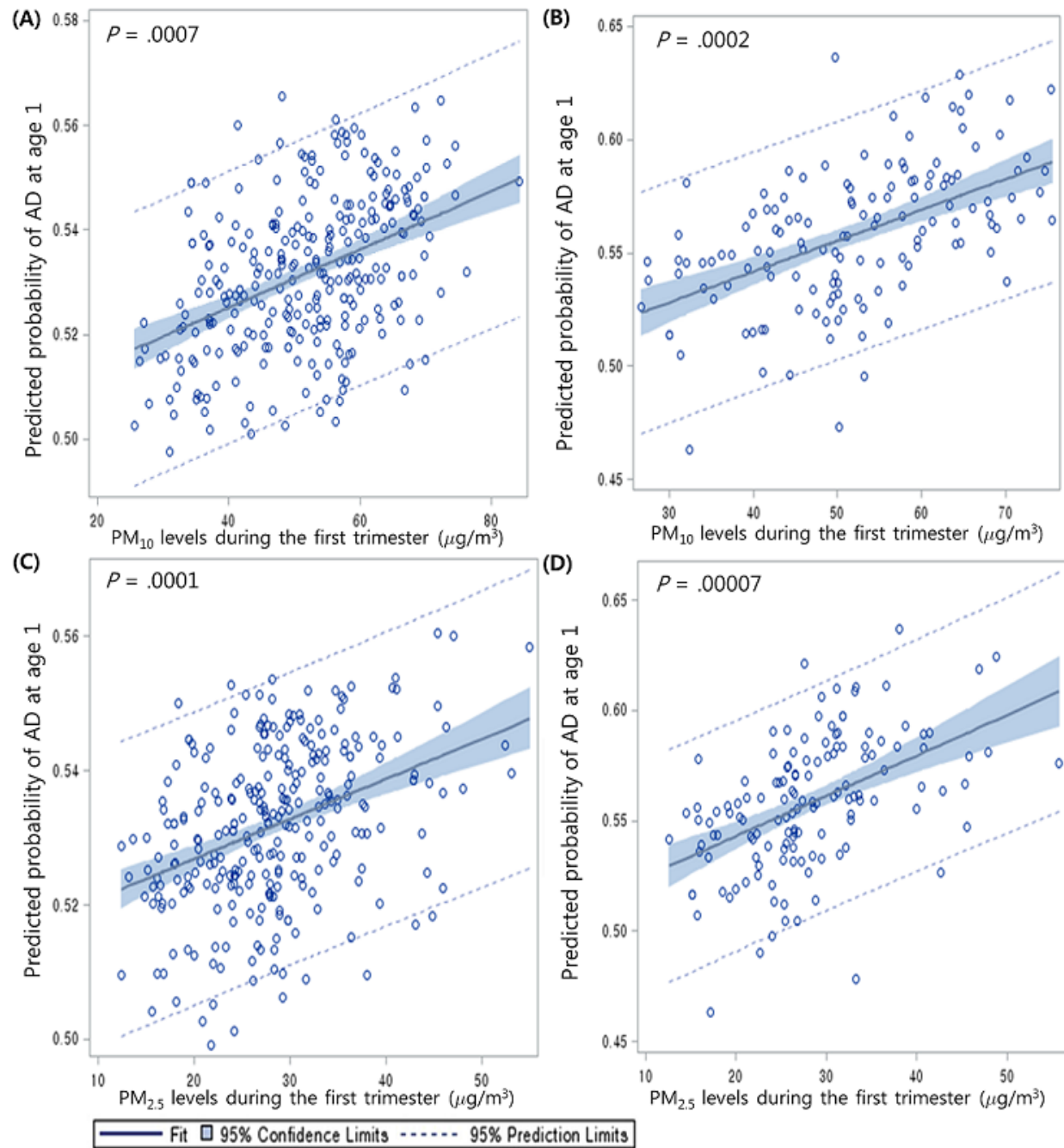
Adjusted for maternal age, gestational age, birth season, maternal educational level, sex, family history of allergic diseases, maternal body mass index during pregnancy, exposure to environmental tobacco smoke, prenatal indoor $PM_{10}/PM_{2.5}$ levels at 36 weeks of gestation, and $PM_{10}/PM_{2.5}$ levels from the prenatal periods to age 1 year, except for PM levels at the specific period.

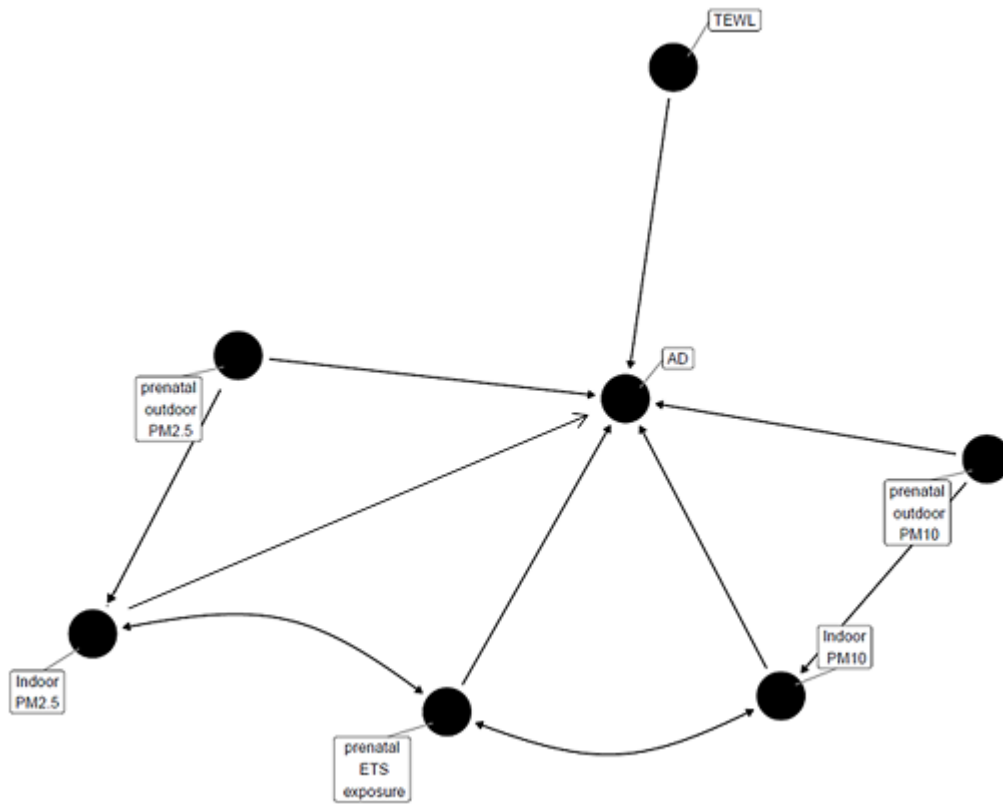
*Significant at the .05 level.

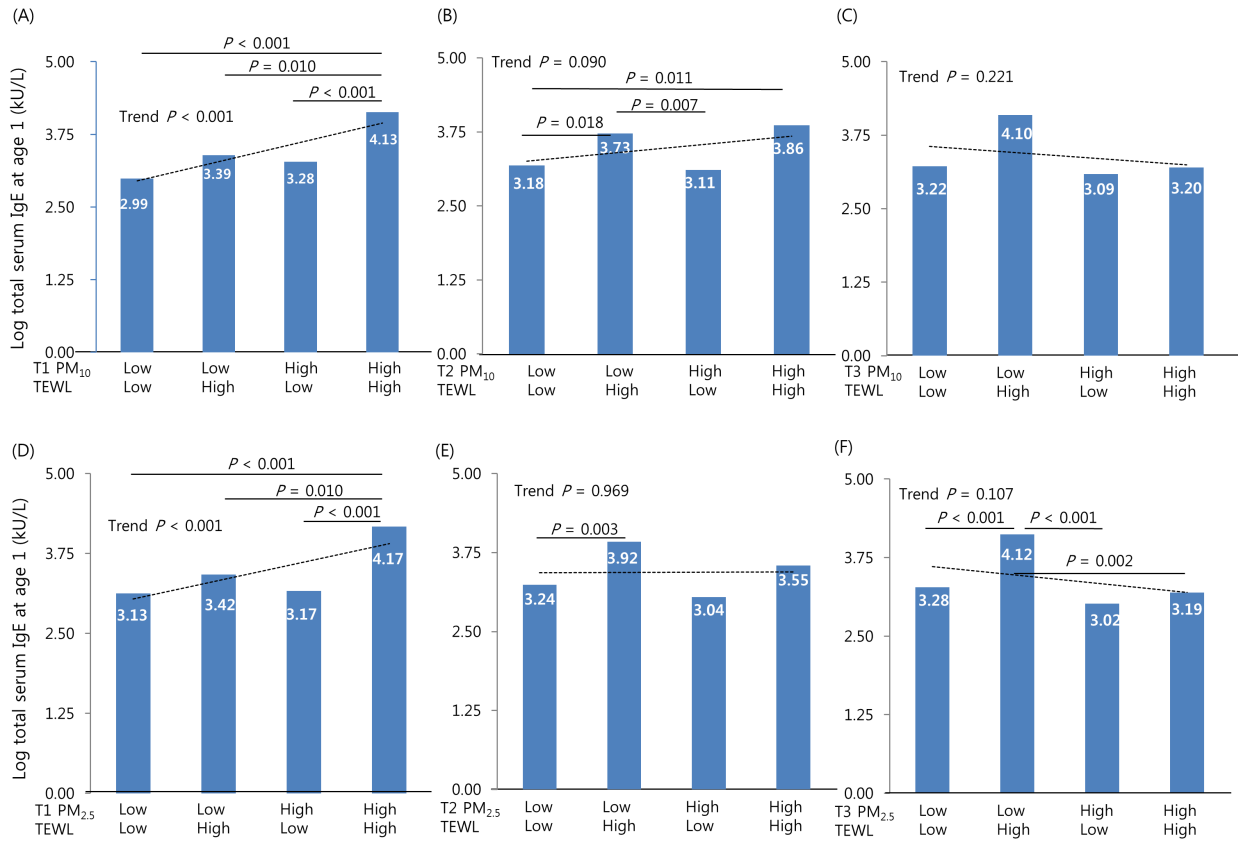
FIGURE 2. Relationship between outdoor $PM_{10}/PM_{2.5}$ levels during the first trimester and predicted probability of AD according to levels of TEWL. Relationship between outdoor PM_{10} levels during the first trimester and predicted probability of AD in infants with high levels of TEWL (A) and those with low TEWL levels (B). Relationship between outdoor $PM_{2.5}$ levels during the first trimester and predicted probability of AD in infants with high levels of TEWL (C) and those with low TEWL levels (D).

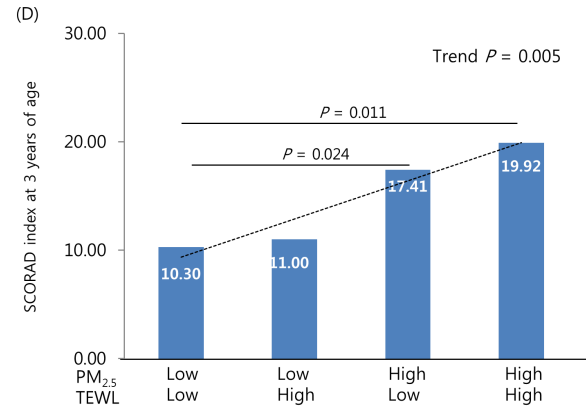
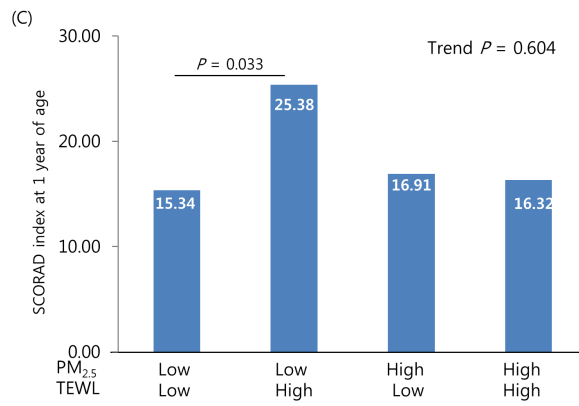
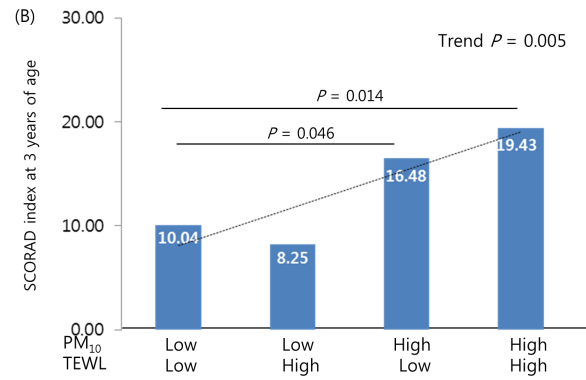
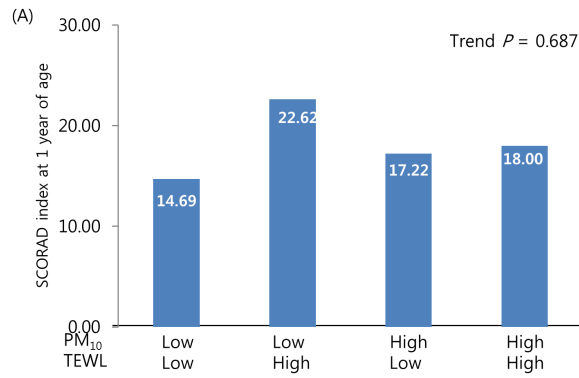
Values were adjusted for maternal age, gestational age, birth season, maternal educational level, sex, family history of allergic diseases, maternal body mass index during pregnancy, exposure to environmental tobacco smoke, prenatal indoor $PM_{10}/PM_{2.5}$ levels at 36 weeks of gestation, and $PM_{10}/PM_{2.5}$ levels from the prenatal periods to age 1 year, except for specific PM levels at the specific period.

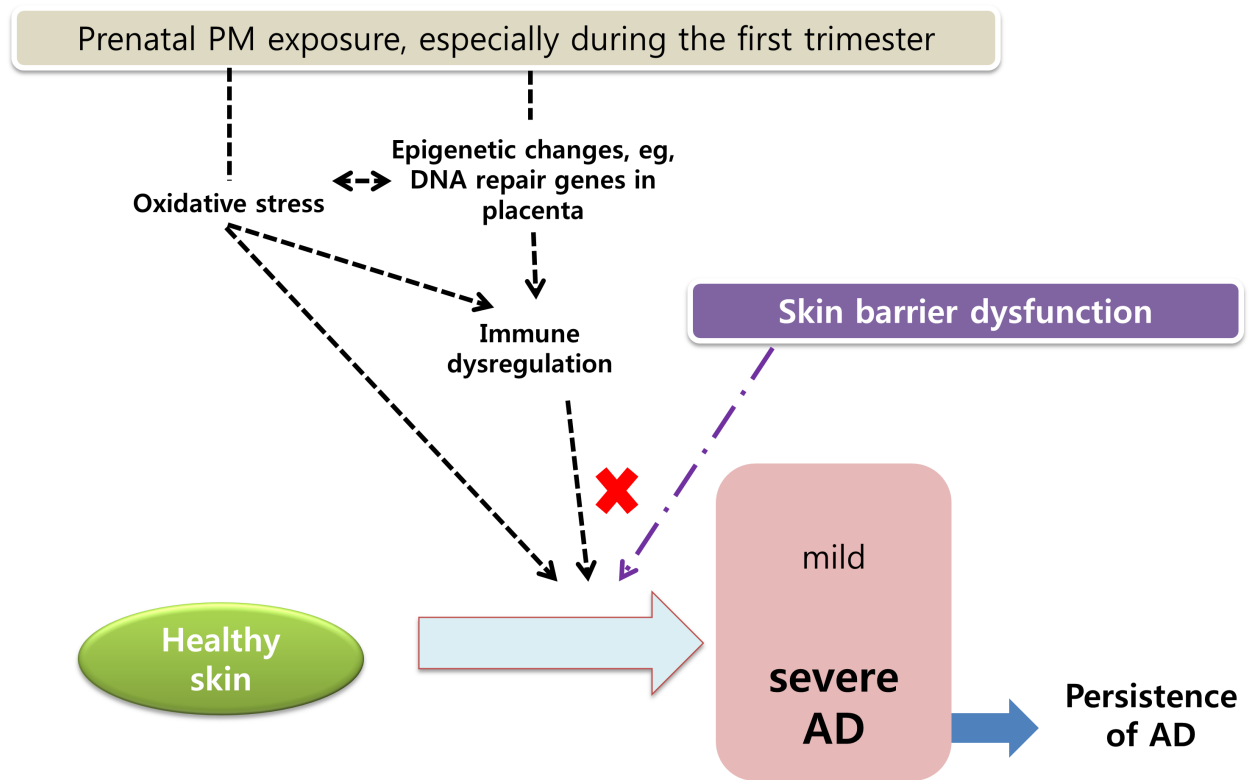












Supplementary Materials

Methods

Measurement of TEWL

TEWL levels were measured on the volar surface of the forearm by applying a probe to the exposed volar skin for approximately 15 seconds, until the measurement was recorded using a Tewameter TM 300 (Courage+Khazaka Electronic, Cologne, Germany). The TEWL measurement was repeated 3 times and the average of the 3 values was recorded. The parents were advised not to apply emollients to the infant's skin for 12 hours before the reading was taken. The infants were brought to a windowless room in which the temperature was set between 20°C and 25°C and humidity was maintained between 30% and 45%.

Measurement of outdoor PM_{10} and $PM_{2.5}$ during the pregnancy

We monitored air pollutants using land use regression (LUR) models and a regulatory monitoring network and used ambient concentrations of PM_{10} and $PM_{2.5}$ measured at the 37 fixed monitoring stations in the study area (Seoul) from the Korean Ministry of Environment (<http://www.airkorea.or.kr/web>). We used centrally and locally available geographic variables as potential predictors. Predictor variables, such as traffic indicators, surrounding land usage, topography, and spatial trends, were computed at each location using ArcGIS version 9.3 (ESRI, Redlands, CA, USA). Multiple linear regression models were built using a supervised forward stepwise procedure. Predictor variables used in the final LUR model for air pollution included the lengths of all roads, traffic intensity on nearest roads, total heavy

duty traffic loads of all roads, and variables representing spatial trends. The models explained 66–69% of the variability in measured PM_{10} and $PM_{2.5}$ levels, and the predicted values fitted well with the measured values, as reported in our previous study.^{E1} The trimester-specific mean concentration of PM_{10} and $PM_{2.5}$ was calculated as the mean values of pollutant concentrations in each week during each trimester.

Measurement of indoor PM_{10} and $PM_{2.5}$ during the pregnancy

The prenatal indoor PM_{10} and $PM_{2.5}$ concentrations were measured in the room, where the pregnant women spent most of their time at 36 weeks of pregnancy, using a particle discriminator (Model GT-331; SIBATA Co., Japan) with a laser light scattering optical particle counter for 5 minutes. Indoor PM_{10} and $PM_{2.5}$ concentrations were measured three times and the mean values were used for evaluation.

Measurement of total serum IgE levels at birth and age 1 year

Total serum IgE levels were measured at birth from cord blood and at 1 year of age using a fluorescent enzyme immunoassay according to manufacturer instructions (AutoCAP System; Phadia AB, Uppsala, Sweden).^{E2} A low-range anti-IgE antibody (range, 0-100 kU/L) was employed for cord blood.^{E2} The lower detection limit for total serum IgE at age 1 was 2.0 kU/L (range, 2-5000 kU/L).^{E2}

Phenotypes of AD

Infants were followed-up until 3 years of age, and phenotypes of AD were classified into 4 categories according to the onset age (early onset, < 2 years of age; late onset, $\geq$ 2 years of age) and persistence of AD (transient, showing improvement of AD symptoms before 2 years of age; persistent, showing symptoms of AD until 3 years of age) as never, early transient, late onset, and early onset persistent.^{E3}

Statistical analysis

To evaluate the associations between prenatal outdoor PM₁₀/PM_{2.5} and AD at age 1, a logistic regression analysis was performed, after separation of the prenatal period into the first (1-13 weeks), second (14-27 weeks), and third (28-40 weeks) trimesters with adjustment for maternal age, gestational age, birth season, maternal educational level, sex, family history of allergic diseases, maternal body mass index during pregnancy, exposure to environmental tobacco smoke, PM₁₀ or PM_{2.5} levels from the prenatal period to age 1 year except at the specified period and prenatal indoor PM₁₀ or PM_{2.5} levels measured at mean 36 weeks of gestation (Figure E1 available in this article's Online Repository at www.jaci-inpractice.org).

Due to the positive correlation between outdoor PM₁₀/PM_{2.5} levels and indoor PM₁₀/PM_{2.5} levels^{E4- E6} and for exclusion of prenatal indoor PM₁₀/PM_{2.5} effects, we adjusted the prenatal indoor PM₁₀/PM_{2.5} levels. To calculate the odds for AD in association with prenatal exposure to PM₁₀/PM_{2.5} combined with skin barrier dysfunction, logistic regression models were used. ANOVA and chi-square tests were used to compare SCORAD score and biomarkers including total serum IgE levels according to PM₁₀/PM_{2.5} exposure levels during the prenatal periods and TEWL levels at age 1. Data analysis was conducted using SPSS 24.0 (IBM Corp.

65 Armonk, IL), with a $P < .05$ considered statistically significant.

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86 **Supplementary Table**87 **Table EI.** Demographic characteristics of the study population

Characteristics, number (%) or mean $\pm$ SD	Participants included in the present study	Excluded in the present study due to lack of information on TEWL levels	<i>P</i> value
Total number, n	468	2633	NA
Gender, male	248 (52.9)	689 (46.9)	.925
Family history of allergic diseases	247 (52.7)	722 (50.2)	.362
Gestational age, weeks	38.9 $\pm$ 1.2	39.2 $\pm$ 1.20	.724
Maternal education level			.612
$\leq$ High school	26 (5.5)	75 (5.2)	
University	351 (74.8)	1060 (73.1)	
Graduate school	92 (19.6)	315 (21.7)	
AD diagnosis at age 1, yes	76 (16.2)	207 (14.7)	.257
AD phenotypes	390 (100.0)	1187 (100.0)	.052
Never	268 (68.7)	847 (71.4)	
Early transient (< 2 years of age)	41 (10.5)	152 (12.8)	
Late onset ($\geq$ 2 years of age)	30 (7.7)	86 (7.2)	
Early onset persistent (both ages 1 year and 3 years)	51 (13.1)	102 (8.6)	

TEWL levels at age 1 year (g/m ² h)	14.74 ± 11.09	NA	NA
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88 AD, atopic dermatitis; NA, not applicable; SD, standard deviation; TEWL, trans-epidermal
89 water loss.

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Supplementary Figure legends

Figure E1. Directed Acyclic Graph (DAG) showing the possible covariates, which may affect the associations between prenatal outdoor PM₁₀/PM_{2.5}, skin barrier dysfunction, and AD.

FIGURE E2. Comparisons of log-transformed cord blood total serum IgE levels according to outdoor PM₁₀ exposure levels during the (A) first, (B) second, and (C) third trimesters. Comparisons of log-transformed cord blood IgE levels according to outdoor PM_{2.5} levels during the (D) first, (E) second, and (F) third trimesters.

FIGURE E3. Comparisons of log-transformed total serum IgE levels at age 1 according to the combination of TEWL levels at age 1 and outdoor PM₁₀ exposure levels during the (A) first, (B) second, and (C) third trimesters. Comparisons of log-transformed total serum IgE levels at age 1 according to the combination of TEWL levels at age 1 and outdoor PM_{2.5} levels during the (D) first, (E) second, and (F) third trimesters. Dotted lines mean trend lines.

FIGURE E4. Comparisons of SCORAD index scores at (A) age 1 and (B) age 3 according to the combination of outdoor PM₁₀ levels during the first trimester and TEWL levels at age 1. Comparisons of SCORAD index scores at (C) age 1 and (D) age 3 according to the

113 combination of outdoor PM_{2.5} exposure levels during the first trimester and TEWL levels.

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115 **Figure E5.** Possible mechanisms for the association between outdoor PM₁₀/PM_{2.5} exposure
116 during the first trimester and skin barrier dysfunction in early life on the development of AD.

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