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Combined effects of traffic-related air pollution, climate factors, and greenness on respiratory disease risk in infants

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Prenatal exposure to climate factors, air pollution, and green space has been linked to respiratory diseases in infants. However, the role of the combined effects of exposure to these factors on respiratory ailments remains unclear. Here we investigate the association of combined exposure to traffic-related air pollution (TRAP), climate factors, and green space during the prenatal period with respiratory diseases in infants. We enrolled 454 participants from the ongoing prospective birth cohort known as the Mothers and Children's Environmental Health study. Data on infant respiratory diseases were collected from parents or guardians. Average exposure values of TRAP, climate factors, and green spaces for the study population were calculated based on geocoded residential addresses. Multiple logistic regression and quantile-based g-calculation models were utilized to examine the association of exposure to environmental factors and green space with respiratory diseases. The combined exposure to climate factors and TRAP during the first trimester of pregnancy was associated with an increased risk of respiratory diseases in infants. High levels of particulate matter with a diameter less than 2.5 μm ($PM_{2.5}$) and temperature increased the risk of respiratory diseases (adjusted odds ratio (AOR): 1.615, 95% confidence interval (CI): 1.001, 2.658). Additionally, the risk of respiratory diseases from exposure to air pollution and temperature was associated with lower tertiles of residential green spaces. The AOR was 1.064 (95% CI: 1.001, 1.133) per 1 μg/m^3 increase in $PM_{2.5}$, 1.057 (95% CI: 1.001, 1.116) per 1 ppb increase in NO_2, and 1.108 (95% CI: 1.001, 1.176) per 1 ℃ increase in temperature. Incorporating green space into the analysis of joint exposure to climate factors and air pollution reduced the risk of respiratory disease. This study proposes that combined exposures to climate factors, TRAP, and green spaces during pregnancy are associated with infant respiratory diseases. Fewer residential green spaces could enhance the association of climate factors and air pollution with respiratory diseases.

Keywords Respiratory, Climate factor, Traffic-related air pollution, Green space, Children, Combined exposure

Abbreviations

AOR	adjusted odds ratio
BMI	body mass index
CI	confidence interval
CMAQ	community multiscale air quality
GIS	geographic information system
LUR	utilizing a land-use regression
MOCEH	Mothers and Children's Environmental Health
NO_2	Nitrogen dioxide
$PM_{2.5}$	particulate matter with a diameter less than 2.5 μm
PMcoarse	particulate matter with a diameter of 2.5 to 10 μm
SD	standard deviation
SHS	secondhand smoke
TRAP	traffic-related air pollution

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Background

Environmental pollution exposure is becoming a major cause of childhood morbidity and mortality, with a particularly negative impact on respiratory diseases[1–3]. Children are more susceptible to pollution because their physiology is different from that of adults, and their immature enzymatic systems make them less likely to detoxify xenobiotics[4,5]. Additionally, because the development of the respiratory system begins during pregnancy, environmental exposures during fetal development often have lasting effects in adult life[6,7].

Traffic-related air pollution (TRAP) encompasses atmospheric contamination arising from both motorized vehicles and non-exhaust traffic sources[8,9]. Recent studies have shown that TRAP and climate change affect respiratory health, particularly worsening respiratory health in older adults and children[8–12]. A US pregnancy cohort study found that elevated concentrations of fine particulate matter during pregnancy were associated with increased risk of asthma in children[11]. Khreis et al. reported that TRAP during childhood adversely affects asthma development[8]. Similarly, a study conducted in Kuala Lumpur found that high levels of TRAP exposure was associated with an increased incidence of respiratory symptoms and impaired lung function in children[9]. Additionally, more than 30% of children will experience cumulative health impacts as the frequency of extreme climate events such as heat and cold waves, floods, and droughts rises, increasing risks to respiratory health[12]. However, another study found that the effect of climate on respiratory mortality was lower when air pollution such as particulate matter and ozone was included[13]. The combined effects on respiratory disease are inconsistent and require further research.

Green spaces distributed around residential areas have been shown to be effective for protecting respiratory health by reducing environmental pollutants[14–16]. A study in southern China found that increased green exposure around residential areas mitigated respiratory mortality through interactions and mediating pathways of air pollutants[17]. However, the effects and mechanisms on the disease are still unclear, with other studies showing no association with green space or providing conflicting results[18–20].

To the best of our knowledge, few studies have explored the interrelationships and joint effects of TRAP, climate change, and green spaces, and none have specifically investigated their effects on respiratory diseases in children using birth cohort data. Therefore, this study aimed to investigate the combined effects of prenatal exposure to air pollution and meteorological factors, as well as the role of surrounding green space, on the risk of respiratory diseases such as asthma, pneumonia, bronchitis, and bronchiolitis in infants.

Methods

Study population

The study population was drawn from the Mothers and Children's Environmental Health (MOCEH) study, the first large-scale prospective cohort study in four regions of Korea. The MOCEH study focused on the investigation of maternal and child diseases and health conditions, the evaluation of fetal growth and development, and the exploration of the associations between these factors and exposure to environmental elements[21]. A total of 1,751 pregnant women with a gestational age of less than 20 weeks were recruited during 2006–2010. Follow-up monitoring of the children's development is ongoing. After excluding lost subjects from follow-up, 1,516 were identified as eligible participants. The study excluded 85 children with birth weight under 2.5 kg or gestational age < 37 weeks. An additional 977 were excluded for incomplete information, including residential address or relocation ($n = 80$), respiratory disease status ($n = 768$), educational level ($n = 11$), household income ($n = 36$), family history of allergy ($n = 12$), maternal body mass index (BMI; $n = 59$), and maternal smoking ($n = 11$). The final selection encompassed 454 participants, and further details are provided in the Supplementary Information (Figure S1). The characteristics of the excluded participants did not differ significantly from those of the study population, thereby supporting the reliability of the data utilized in this study (Table S1). All participants in the MOCEH study provided informed consent before enrollment. This study received ethical approval from the Institutional Review Boards of Dankook University Hospital, Ulsan University Hospital, and Ewha Womans University. All studies were carried out in accordance with relevant guidelines and regulations. This research was performed in accordance with the Declaration of Helsinki.

Climate factors and air pollution assessment

To determine each participant's level of TRAP exposure in this study, we estimated pollutant concentrations at their residential locations by applying a land use regression (LUR) model based on standardized procedures and precise address geocoding. This assessment leveraged values from the Korean Ministry of Environment's atmospheric measurement station, incorporating predictive variables such as topography, land usage, spatial trends, and traffic indicators. Model results for nitrogen dioxide ($NO_{2)}$ and particulate matter with a diameter less than 10 μm (PM_{10}) yielded adjusted R-squared values of 0.79 and 0.69, respectively. These show a strong correlation between the predicted and observed values, as previously documented[22,23]. In Korea, particulate matter with a diameter less than 2.5 μm ($PM_{2.5}$) began to be measured in 2015; thus, LUR analysis for this factor could not be performed due to the lack of requisite air pollution station data. Therefore, we estimated $PM_{2.5}$ exposure through community multiscale air quality (CMAQ) modeling, a three-dimensional photochemical transport framework that processes atmospheric emission information. Previous research provided detailed information on the CMAQ air quality numerical modeling[24]. $PM_{2.5}$ concentrations for each study subject were derived through kriging interpolation using a geographic information system tool. Performance evaluation of the CMAQ model showed an R-squared value of 0.64 and a root mean squared error of 4.17. PMcoarse was derived by subtracting the $PM_{2.5}$ mass concentration from that of PM_{10}. Given that PM_{10} encompasses $PM_{2.5}$, $PM_{2.5}$ and PMcoarse were included in the analysis to evaluate their respective associations with disease outcomes.

Climate factors, including minimum, maximum, and average temperatures, and relative humidity were analyzed by processing data provided by the Korea Meteorological Administration. Participant's exposure levels to TRAP and climate factors were calculated based on date of birth and gestational age. After computing the daily average values, the exposure measures for each pregnant woman during the first, second, and third trimesters, as well as the entire pregnancy, were analyzed.

Residential greenness assessment

Residential green spaces were evaluated utilizing the Korean Ministry of Environment's Land-Cover Map, which accurately represents land cover across Korea. Thematic maps were derived from the National Aeronautics and Space Administration's Landsat image data and Korea's Arirang satellite imagery. Following methods detailed in previous studies[25], maps depicting grasslands, forest areas, and parks were extracted employing geographic information system (GIS) tools (ArcGIS Pro version 2.7.0.). These were used to quantify the green space within 100, 200, 300, and 500 m buffers surrounding the subjects' residences. Individual green space exposure during pregnancy was evaluated using GIS-based spatial analysis of residential locations, which incorporated geocoded address data for each participant.

Health outcome

Information regarding respiratory diseases diagnosed by physicians at the age of six months was gathered through a questionnaire administered to the children's parents or primary caregivers. The occurrence of respiratory diseases was identified through a positive response to the inquiry "Has your child ever been diagnosed by a medical doctor with respiratory diseases such as asthma, bronchitis, pneumonia, and bronchiolitis?" A diagnosis of respiratory disease was considered confirmed if any of these ailments was present. Although questions were formulated for each specific respiratory disease, the study had a limited number of cases involving respiratory diseases among six-month-old infants. Consequently, respiratory-related diseases were grouped and analyzed.

Covariates

Covariates included in the models were gestational age (in weeks), maternal age (in years), infant sex, maternal educational level (either less than university or university and above), BMI, parental history of allergies, season of birth, exposure to environmental tobacco smoke, and monthly household income category (below $2000, $2000–4000, and above $4000). Gestational age was determined as the interval between the date of the last menstrual period and the date of delivery, as documented in medical records. Other variables were assessed via interviews and questionnaires conducted by trained personnel with primary caregiver. Exposure to environmental tobacco smoke (ETS) was defined based on whether any household member smoked indoors during pregnancy. Participants who responded affirmatively were classified as exposed to ETS. Adjusted covariates were selected based on established or suspected confounders identified in previous literature and known risk factors for the outcomes[8–13].

Statistical analysis

The frequencies and values of specific features were analyzed in relation to the children's respiratory status using the chi-square and *t*-test. Multiple logistic regression models were employed to explore associations between respiratory diseases, TRAP, and climate factors or green area levels. To assess the risk of respiratory diseases stemming from combined exposure to TRAP and climate factors, the variables were stratified by TRAP and climate change influences and then recombined and evaluated for unit increases. Based on the levels of residential green space, a stratified analysis was conducted to pinpoint the connection between the combined exposure to climate factors, TRAP during different windows of pregnancy (first, second, and third trimesters), and resultant respiratory diseases in infants. A quantile-based g-computation analysis was performed to complement the combined exposure assessment and to address potential collinearity. The method integrated the adaptability of g-computation as an estimation approach with the direct inference provided by weighted quantile sum regression. Environmental composite exposure effects were estimated using g-computation through generalized linear models to estimate causal effects[26].

Several sensitivity analyses were conducted to assess the robustness of the associations between climate factors, TRAP, greenness exposure, and respiratory disease. First, to verify the consistency of greenness benefits

regardless of model flexibility and buffer size, greenness exposures within 100 m, 200 m, and 300 m buffers were compared to the primary exposure at 500 m using a flexible spatial model based on Global Positioning System (GPS). Second, to investigate the interactions between climate factors, TRAP, and green space, an interaction term was included for each paired exposure and analyzed. Third, given the observed significant differences in secondhand smoke (SHS) exposure between participants with and without respiratory diseases, we further investigated potential effect modification by including interaction terms between SHS exposure and both climatic factors and air pollution in the models. The analyses were conducted using STATA (version 17, Stata Corp, USA), R (version 4.2.1), and ArcGIS pro 2.7.0.

Results

Among the 454 participants, 75 were six-month-old infants with a history of diagnosis of respiratory diseases. These included 4 cases of asthma, 38 cases of pneumonia, 35 cases of bronchitis, and 37 cases of bronchiolitis, with 39 duplicate cases. The specific characteristics of the study subjects, both with and without respiratory diseases, are consolidated in Table 1. The average maternal age was approximately 29 years. During pregnancy, 63% of the mothers encountered secondhand smoke, a rate greater among those whose infants had respiratory diseases. The characteristics of the excluded participants did not differ significantly from those of the study population (Table S1). Data on maternal exposure to different environmental factors and gestational stages is available in Supplementary Tables (Table S2). The mean exposures (standard deviation, SD) during pregnancy were 29.9 (5.10) $\mu g/m^3$ for $PM_{2.5}$, 24.04 (8.79) $\mu g/m^3$ for PMcoarse, and 24.7 (8.01) ppb for NO_2.

The associations between respiratory diseases and exposures to climatic elements, air pollutants, and green spaces during pregnancy are detailed in Fig. 1. Single-pollutant models employing multivariable logistic regression indicate that the risk of respiratory diseases is associated with exposures to $PM_{2.5}$, particulate matter with a diameter of 2.5 to 10 µm (PMcoarse), and NO_2 during the first trimester of pregnancy. The adjusted odds ratio (AOR) (95% confidence interval (CI)) was 1.039 (1.004, 1.076) per 1 $\mu g/m^3$ increment in $PM_{2.5}$, 1.024 (1.003, 1.046) per 1 $\mu g/m^3$ increment in PMcoarse, 1.032 (1.001, 1.064) per 1 ppb increase in NO_2, and 1.021 (1.001, 1.056 per 1 ℃ increment in temperature. The associations between respiratory diseases and exposure to climate variables and green spaces in different trimesters are shown. Figure S2 delineates the correlation between climate factors, air pollutants, and greenness, with the correlation coefficient ranging from −0.23 to 0.7.

	Total (n = 454)	Respiratory disease at an age of 6 months		p-value[a]
		No (n = 379)	Yes (n = 75)	
Maternal				
Age (years), mean(SD)	**28.5 (8.0)**	**28.8 (7.6)**	**26.9 (9.8)**	**0.071[b]**
< 30	**207 (45.6)**	**168 (44.3)**	**39 (52.0)**	**0.476[c]**
30–34	**206 (45.4)**	**176 (46.4)**	**30 (40.0)**	
≥ 35	**41 (9.0)**	**35 (9.2)**	**6 (8.0)**	
Education, *n*(%)				
< university	**243 (53.5)**	**204 (53.8)**	**39 (52.0)**	**0.772**
≥university	**211 (46.5)**	**175 (46.2)**	**36 (48.0)**	
Income per month, *n*(%)				
<$2000	**104 (22.9)**	**92 (24.3)**	**12 (16.0)**	**0.243**
$2000–4000	**279 61.5)**	**227 (59.9)**	**52 (69.3)**	
>$4000	**71 (15.6)**	**60 (15.8)**	**11 (14.7)**	
Prepregnancy BMI, mean (SD)	**21.3 (3.1)**	**21.4 (3.1)**	**21.1 (2.8)**	**0.489**
History of allergy, *n*(%)				
No	**418 (93.3)**	**351 (94.1)**	**67 (89.3)**	**0.132**
Yes	**30 (6.7)**	**22 (5.9)**	**8(10.7)**	
Exposure to SHS, *n*(%)				
No	**286 (63.0)**	**238 (62.8)**	**48 (64.0)**	**0.039**
Yes	**168 (37.0)**	**141 (37.2)**	**27 (36.0)**	
Gestational age (weeks), mean (SD)	**39.1 (1.1)**	**39.1 (1.1)**	**39.0 (1.2)**	**0.583**
Infant				
Sex, *n*(%)				
Male	**250 (55.1)**	**203 (53.6)**	**47 (62.7)**	**0.148**
Female	**204 (44.9)**	**176 (46.4)**	**28 (37.3)**	
Birth weight (grams), mean (SD)	**3329 (374.5)**	**3331 (375.7)**	**3315 (370.4)**	**0.725**

Table 1. Baseline characteristics of study subjects. Note: BMI, body mass index; SD, standard deviation; SHS, secondhand smoke. [a] Two-sided chi-square and t-test where appropriate. [b] p value calculated using the t-test for age (continuous variable). [c] p value calculated using the chi-square test for age (three categories).

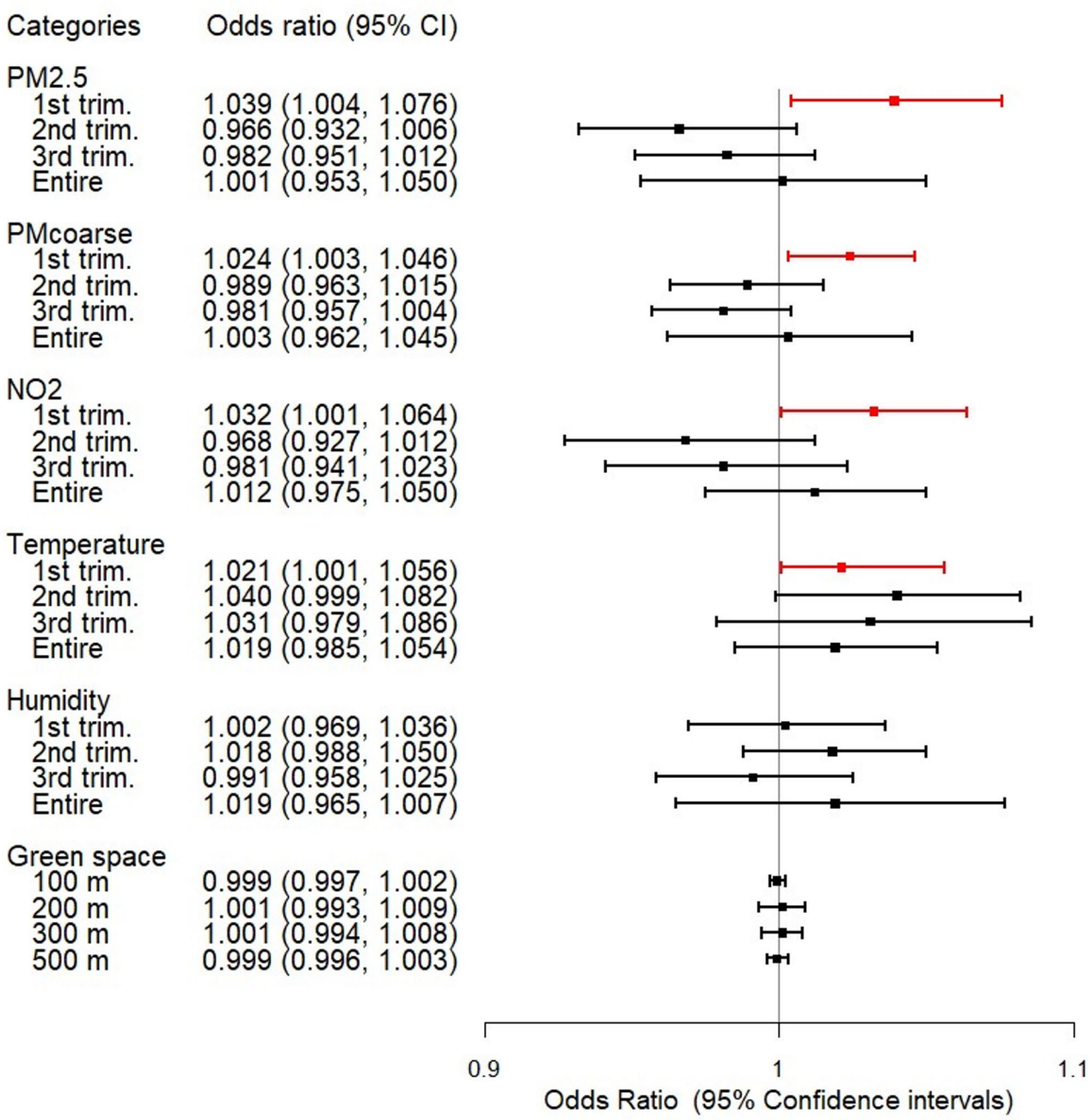


Fig. 1. Risk of respiratory diseases in infants with prenatal exposure to traffic-related air pollution, climate factors, and residential green space. Multiple logistic regression models were employed to explore associations between respiratory diseases, air pollution, and climate factors or green area levels. The models were adjusted for maternal age, education, income, BMI, gestational age, exposure to secondhand smoke, birth weight, sex, and season of birth. Abbreviations: trim., trimester.

Figure 2 illustrates the combined exposure effects of climate variables and TRAP on the risk of respiratory diseases, as determined by a stratified analysis. Both temperature and air pollution were categorized into tertiles, with subsequent analyses conducted for each tertile group. The risk of respiratory diseases increased when $PM_{2.5}$ concentrations exceeded 32.9 μg/m^3 and temperatures were greater than 17.1 ℃, resulting in an AOR of 1.615 (95% CI: 1.001, 2.658). The combined exposure to PMcoarse and climate factors was not associated with respiratory diseases (Figure S3).

The risk of respiratory diseases decreased when NO_2 (< 19.4 ppb) and temperature (< 9.7 ℃) were at low levels. The AOR was 0.702 (95% CI: 0.501, 0.983). The combined exposure to NO_2 and humidity was not associated with respiratory diseases (Fig. 3).

Table 2 shows the association between the risk of respiratory diseases and exposure to air pollution and temperature in regions with lower tertiles of residential green areas within a 500-meter buffer zone. The AOR

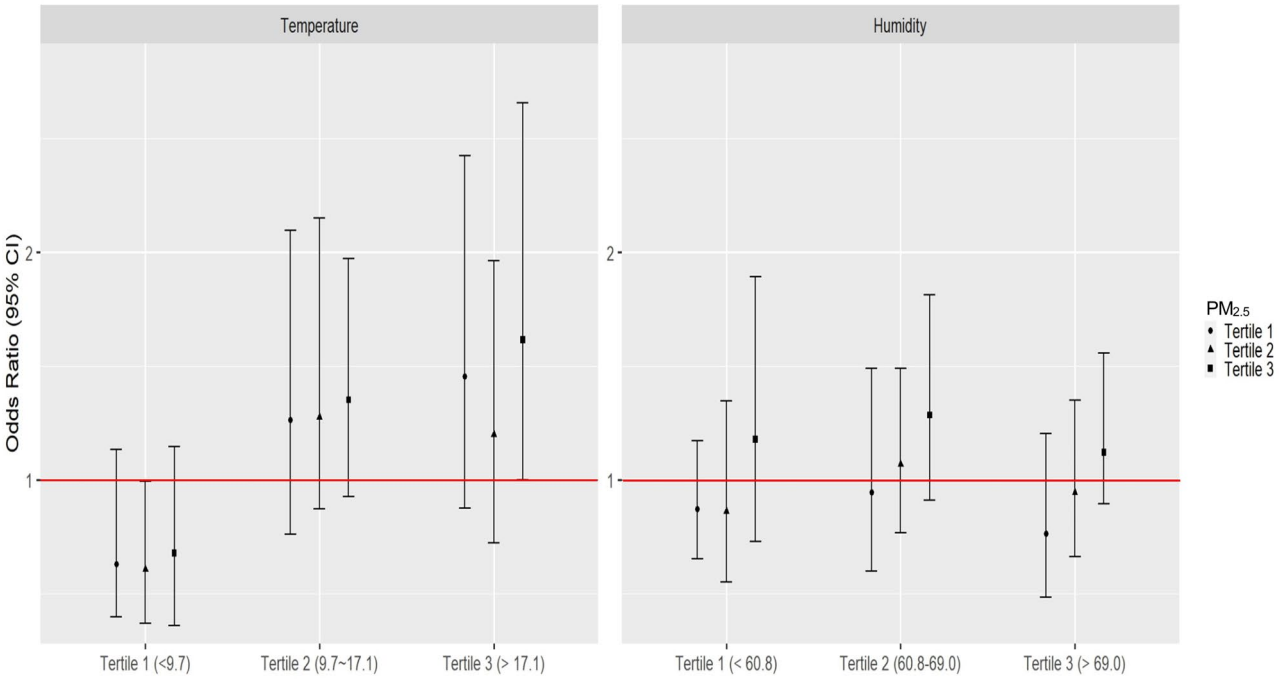


Fig. 2. Effects of combined exposure of climate factors and $PM_{2.5}$ on respiratory disease risk in infants aged six months during the first trimester of pregnancy. (A) Stratified analysis by temperature, defining tertile 1 as < 9.7 °C, tertile 2 as 9.7–17.1 °C, and tertile 3 as > 17.1 °C. (B) Stratified analysis by humidity, categorizing tertile 1 as < 60.8%, tertile 2 as 60.8–69.0%, and tertile 3 as > 69.0%. The straight line with a circle, triangle, and square marks indicate $PM_{2.5}$ concentrations < 25.7, 25.7–32.9, and > 32.9 μg/m3, respectively. The Y-axis represents the AOR (95% CI) for the combined exposure effect of climate variables and air pollution on respiratory disease risk. Multiple logistic regression models were used to explore the association between respiratory diseases and combined exposure to $PM_{2.5}$ and climate factors. The models were adjusted for maternal age, education, income, BMI, gestational age, exposure to secondhand smoke, birth weight, sex, and season of birth.

(95% CI) was 1.064 (95% CI: 1.001, 1.133) per 1 $\mu g/m^3$ increase in $PM_{2.5}$, 1.057 (95% CI: 1.001, 1.116) per 1 ppb increase in NO_2, and 1.108 (95% CI: 1.001, 1.176) per 1 ℃ increase in temperature.

Table 3 shows the joint effects of mixture exposures of climate factors, TRAP, and green spaces on respiratory disease, and quintile-based g-computation models produced approximate risk estimates. Each quintile increase in exposure to air pollutants and climate factors was associated with an AOR of 1.601 (95% CI: 1.021, 2.532) for respiratory disease in children. When green space was additionally included in air pollution and climate factors, the composite exposure was associated with an AOR of 1.383 (95% CI: 1.325, 1.858).

Additionally, to assess the combined impact of climatic factors, TRAP, and green space on the risk of respiratory disease, each exposure variable was categorized into tertiles. The results showed that living in areas with limited green space, higher NO_2 levels, and elevated temperatures was associated with increased respiratory disease risk (Table S3). Sensitivity analysis indicated that our results were robust. Examination of the relationship between green space and TRAP, temperature, and respiratory diseases with buffers within 100, 200, and 300 m from residential areas yielded similar findings to the 500-m buffer (Table S4 and Table S5). Additionally, a continuous interaction term was included in analysis to investigate the interaction between climate factors, air pollution, and green spaces. The association was not significant, supporting exclusion of the interaction term (Table S6). Interaction analyses between SHS and environmental variables showed no significant effect modification on respiratory health (Table S7).

Discussion

Prenatal exposure to TRAP, including $PM_{2.5}$, PMcoarse, and NO_2, as well as climatic factors such as ambient temperature and humidity, was associated with an increased risk of respiratory diseases in children at six years of age. After stratifying the climate factors and air pollution and examining their combination for each tertile, it became apparent that combined exposure to TRAP and climate factors in the first trimester of pregnancy was associated with a higher risk of respiratory diseases in children at age 6 in the higher tertile. In addition, exposure to high tertiles of $PM_{2.5}$ and temperature and to the low tertile of green space increased the risk of respiratory disease. As a result of complex exposure analysis of air pollution and climate factors, the impact on respiratory diseases was high, and the risk decreased when additional green space was included. Our study showed evidence for the impact of combined prenatal exposure to climate factors, air pollution, and green space on respiratory diseases in children.

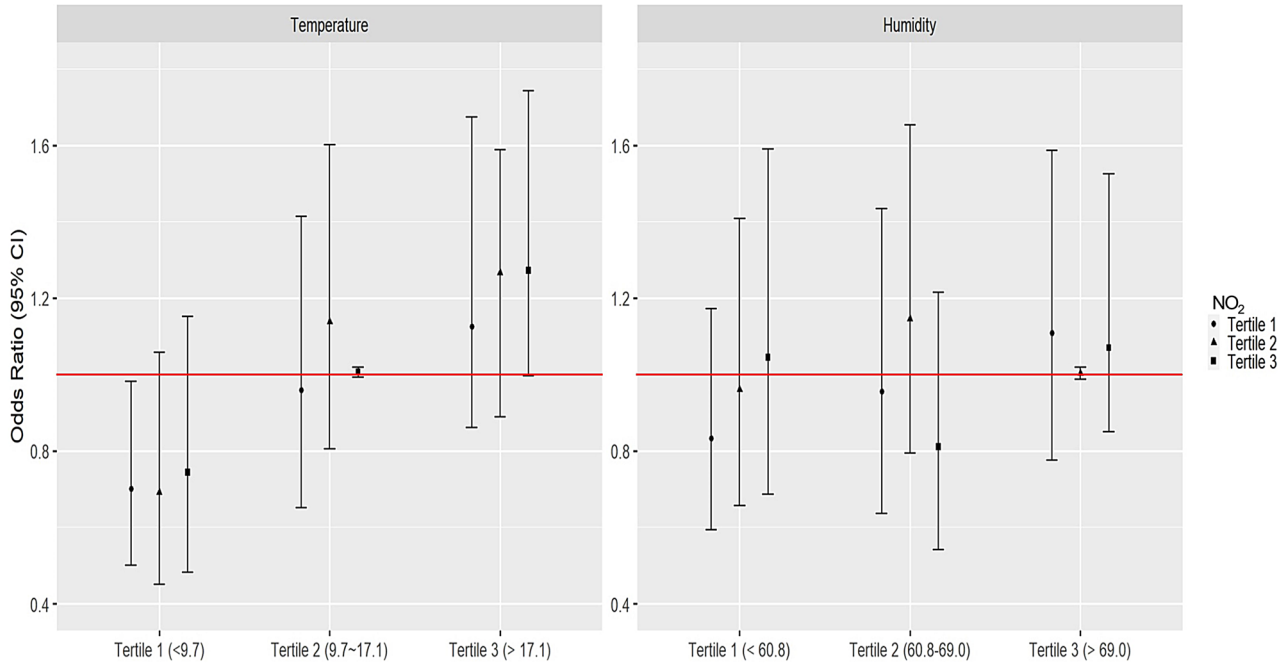


Fig. 3. Effects of combined exposure of climate factors and NO_2 on respiratory disease risk in infants aged six months during the first trimester of pregnancy. (A) Stratified analysis by temperature, with tertile 1 defined as < 9.7 °C, tertile 2 as 9.7–17.1 °C, and tertile 3 as > 17.1 °C. (B) Stratified analysis by humidity, where tertile 1 is < 60.8%, tertile 2 is 60.8–69.0%, and tertile 3 is > 69.0%. The straight line with a circle mark indicates NO_2 < 19.4 ppb, the triangle mark indicates 19.4–23.5 ppb, and the square mark indicates > 23.5 ppb. The Y-axis depicts the AOR (95% CI) for the combined exposure effect of climate variables and air pollution on respiratory disease risk. Multiple logistic regression models were used to explore the association between respiratory diseases and combined exposure to NO_2 and climate factors. The models were adjusted for maternal age, education, income, BMI, gestational age, exposure to secondhand smoke, birth weight, sex, and season of birth.

Green space (m^2)	*n*	Respiratory diseases, adjusted OR (95% CI)				
		$PM_{2.5}$ ($\mu g/m^3$)	PMcoarse ($\mu g/m^3$)	NO_2 (ppb)	Temperature (℃)	Humidity (%)
Tertile 1 (< 158.5)	152	1.064 (1.001–1.133)	1.042 (0.988–1.099)	1.057 (1.001–1.116)	1.084 (1.001–1.176)	1.026 (0.960–1.095)
Tertile 2 (158.5–444.8)	**151**	**1.027 (0.999–1.147)**	**1.029 (0.976–1.085)**	**1.049 (0.943–1.166)**	**1.070 (0.976–1.172)**	**1.025 (0.962–1.091)**
Tertile 3 (> 444.8)	**151**	**1.012 (0.956–1.071)**	**1.003 (0.958–1.051)**	**0.996 (0.313–1.858)**	**1.063 (0.989–1.141)**	**1.015 (0.958–1.076)**

Table 2. Risk of respiratory diseases in infants with exposure to traffic-related air pollution and climate factors by level of residential green area. Note: Adjusted for maternal age, education, income, BMI, gestational age, exposure to secondhand smoke, birth weight, infant sex, and season of birth. CI, confidence interval; NO_2, nitrogen dioxide; OR, odds ratio; $PM_{2.5}$, particulate matter with a diameter less than 2.5 μm, PMcoarse, particulate matter with a diameter between 2.5–10 μm.

This study demonstrates that prenatal exposure to TRAP is associated with increased odds of respiratory diseases in six-month-old infants. This aligns with the results of a study performed in Spain, which monitored 352 infants from birth to one year of age, indicating a positive association between wheezing and prenatal NO_2 exposure[27]. Moreover, the association between asthma during preschool (0–5 years) and prenatal NO_2 exposure was identified in a Canadian cohort of 58,306 children[28]. Specific maternal NO_2 exposure, especially during the first trimester of pregnancy, was linked to a heightened risk of developing rhinitis, asthma, and eczema in infants[29]. A cohort study in the United States involving 708 children (0.3–2 years) documented that exposure to $PM_{2.5}$ was associated with wheezing[30], and a significant reduction in lung function was attributed to prenatal exposure to PM_{10} from road traffic[31]. Several recent reviews have underscored significant links between early-life exposure to TRAP and the onset of asthma in childhood[8,32]. Nevertheless, recent studies involving Chinese preschool children found no association between asthma and prenatal NO_2 exposure[33,34], a discrepancy that may stem from variations in the study population, exposure assessment, and outcome definitions.

Exposure variables	Joint effect Adjusted odds ratio (95% CI)
$PM_{2.5}$ + PMcrs + NO_2	1.383 (1.325, 1.858)
Temperature + Humidity	1.472 (0.998, 1.472)
$PM_{2.5}$ + PMcrs + NO_2 + Temperature + Humidity	1.601 (1.021, 2.532)
$PM_{2.5}$ + PMcrs + NO_2 + Temperature + Humidity + NDVI	1.445 (0.836, 2.497)

Table 3. The joint effect of exposures t climate factors, traffic-related air pollution, and green spaces on the childhood respiratory system by quantile-based g-computation models. Note: Adjusted for maternal age, education, income, BMI, gestational age, exposure to secondhand smoke, birth weight, infant sex, and season of birth. CI, confidence interval; NDVI, Normalized Difference Vegetation Index; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with a diameter less than 2.5 μm; PMcrs, particulate matter with a diameter of 2.5 to 10 μm.

The present study has delineated an association between respiratory diseases in infants aged six months and elevated mean ambient temperature during the first trimester of pregnancy. This relationship has been infrequently explored in previous research, with limited studies examining the influence of temperature during pregnancy on subsequent respiratory conditions in children. Our findings align with a cohort study conducted on 2,598 preschoolers in China, which indicated that high temperature exposure during the first trimester was correlated with asthma (AOR = 2.33; 95% CI: 1.11–4.90)[35]. Discussing the prenatal impact of temperature on infant respiratory health is challenging given the paucity of targeted research. However, existing studies focusing on short-term and postnatal effects of ambient temperature offer valuable insights. Several studies on the climatic risk factor for respiratory diseases, particularly asthma, have consistently shown that both high and low temperatures contribute to increased morbidity[36,37]. A time-series analysis from Hong Kong revealed a heightened risk of hospitalization for asthma when the average daily temperature rose above 27 °C during the hot season[38]. Moreover, an investigation in Brisbane, Australia, demonstrated that hot weather's effects on children's emergency room visits for asthma in children were immediate and significant[37].

Despite these findings, several studies have not established a connection between short-term temperature exposure and asthma-related outcomes in several global locations, including Sweden[39], Japan[40], and China[41]. The current study adds to this discourse by identifying the prenatal effect of ambient temperature on respiratory diseases, providing evidence of temperature-triggered respiratory conditions.

We found that combined exposure to meteorological factors and TRAP during pregnancy increases respiratory disease in children. On cross-analyzing $PM_{2.5}$ and average temperature into tertiles, diseases increased when both $PM_{2.5}$ and average temperature were high. Additionally, combined exposure to climate factors and air pollution such as temperature, humidity, $PM_{2.5}$, PMcoarse, and NO_2 increased the risk of respiratory disease. Many studies have explored the effects of air pollution or climate factors on the disease, but there is not much research on the combined effects of factors on respiratory diseases. In particular, there is little research on the joint effects of environmental factors during pregnancy. A study by Yang et al. (2023)[42] suggested that the interaction of PM_{10} and SO_2 exposure during pregnancy with temperature and daily temperature changes was associated with the development of childhood pneumonia. A cohort study conducted in Changsha, China found that low and high temperatures during pregnancy each interacted with air pollution exposure during pregnancy to increase the impact on childhood asthma[36]. Our study provides further evidence for the impact of combined prenatal exposure to meteorological factors and air pollutants on respiratory disease in children.

The link between environmental pollution, such as climate factors and air pollution, and respiratory health can be understood through biological plausibility. Air pollution causes oxidative stress and airway inflammation, changes in lung endothelial cells, and leads to respiratory complications[43]. Prolonged exposure to heat can dilate blood vessels and activate thermoregulatory responses such as increased ventilation rate and lung volume. Such heat exposure has been shown to exacerbate airway hyperresponsiveness and augment oxidative stress within pulmonary tissues, thereby contributing to airway remodeling and the aggravation of asthma-related symptoms[44]. Furthermore, as the respiratory system serves as the primary route for the entry of airborne pollutants, heightened ventilation in hot environments may result in greater overall pollutant[45,46]. The immature respiratory system and limited adaptability of children in infancy may further enhance their vulnerability to air pollution and temperature changes[47]. The first trimester of pregnancy is a critical period for respiratory system development. During weeks 4 and 7 post-conception, primary lung buds form and branch, establishing the basic framework of the pulmonary lobular structure by the end of week five. By weeks 10–11, fetal breathing movements begin, facilitating further lung maturation. Environmental or physiological disturbances during this formative stage may result in long-lasting structural consequences[48].

On the other hand, green environments have been found to play a role in regulating climate factors, reducing exposure to harmful pollutants, and lowering temperature or maintaining appropriate humidity[42,49–51]. This study showed that the impact of air pollution and temperature on respiratory diseases was higher in areas with less green space within a 500-m radius from residential areas. Even when analyzed using a complex exposure method, green space was found to play a protective role against respiratory disease risk related to air pollution and temperature. A study in Taipei found that when the green space such as green structures is low, the mortality rate of respiratory diseases such as pneumonia and chronic lower respiratory disease increases due to an increase in air pollutants, and when the ratio of green space is high, the mortality rate from diseases decreases[14]. A study of children under 5 years of age in Hanoi, Vietnam demonstrated that green spaces lower local temperatures,

reducing the impact of heat on respiratory diseases[52]. These studies echo the findings in this study, which found that the size of green spaces affects respiratory disease due to exposure to air pollution and high temperature. However, a New York City birth cohort study showed conflicting results, suggesting that increased tree canopy coverage may increase the incidence of asthma or allergic diseases due to sources such as pollen[53].

Green spaces can strengthen the immune system by releasing antibacterial organic compounds such as phytoncides[54], and can alleviate oxidative stress by filtering out pollutants[55,56]. In a study of a group of lung disease patients in Japan, a significant decrease in inflammatory cytokines was observed in the forest-exposed group[57]. Surrounding green spaces may enhance local air quality through the absorption and filtration of pollutants, contribute to the moderation of microclimatic conditions by lowering ambient temperatures, and potentially mitigate the risk of respiratory diseases by modulating inflammatory processes[58].

The key strength of this study resides in its design as a prospective birth cohort study initiated from early pregnancy. To the best of our knowledge, this represents the first study exploring the effect of exposure to a combination of climatic elements, air pollution, and green spaces on respiratory diseases. The synergistic exposure effects of climatic variables and air pollution were analyzed through a stratification analysis and quantile g-computation. Additional advantages include leveraging LUR and CMAQ models to objectively estimate exposure at the individual level and capture pollution variability at a granular scale.

Certain limitations should be noted for the interpretation of our findings. First, the diagnosis of respiratory diseases was contingent on interviews and answers to questionnaires completed by the primary caregiver, which might suffer self-reporting bias. Second, a joint effect analysis, employing the quantile g-computation model, enables consideration of the nonlinear correlation between exposure level and respiratory incidence and the effects of a combined exposure, but not the variability of each exposure or actual effects. Third, this study focused specifically on temperature and relative humidity as climate exposure variables. Nonetheless, these parameters, as well as air pollution, may be influenced by additional meteorological factors such as wind speed, solar radiation, precipitation, heatwaves, and cold spells. Therefore, future research should comprehensively account for these variables when evaluating climate-related risks of respiratory diseases in children. Fourth, because the study focused on three specific Korean cities (Seoul, Cheonan, and Ulsan), a careful analysis is required prior to extrapolating the results to other Korean urban areas. Fifth, owing to the spatial and temporal resolution of the available greenness data, residential green space exposure was evaluated for the entire pregnancy period rather than stratified by trimester. Future analyses will aim to improve exposure assessment by utilizing greenness data with higher temporal resolution. Finally, potential misclassification of exposure may exist, as our LUR and CMAQ models were estimated using residential addresses, not accounting for exposure when children were outside their areas of residence.

Conclusions

The findings from this study suggest that simultaneous exposure to TRAP, climate factors, and residential green areas during pregnancy has an association with respiratory diseases in infants. A reduced presence of green space in residential areas may amplify the relationship between exposure to air pollutants and climate factors and the incidence of respiratory diseases. Further research is imperative to elucidate the mechanism by which green space modulates the effects of respiratory diseases caused by the combined influence of climate and air pollution.

Data availability

The datasets generated or analysed during the current study are not publicly available due to ethical considerations for study participants, but are available from the corresponding author on reasonable request.

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Author contributions
JYL, SL, and JHL planned and conceived the study. YH, HP, YK, MH, and EH contributed to the initial cohort data collection. SL, JO, WL, EK, and JYL conceived the research method and performed statistical analysis of the data. DL, SS, MP, and JYL were responsible for drafting the primary manuscript. JO, WL, DL, YH, HP, YK, MH, and EH performed the interpretation of study analysis results. JYL, SL, MP, and JHL revised and finalized the manuscript. All authors contributed to the completion of the manuscript and reviewed and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This study received ethical approval from the Institutional Review Boards of Dankook University Hospital (IRB No. 2011-09-0340), Ulsan University Hospital (IRB No. 06–29), and Ewha Womans University (IRB No. 12-07B-15).

Additional information
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