1 **Age-specific effects of ozone on pneumonia in Korean children and adolescents: A**
2 **nationwide time-series study**

3
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34

35 **AUTHOR CONTRIBUTION**

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Abstract

OBJECTIVES: To estimate the age-specific effects of 8-hour maximum ozone levels on pneumonia in children and adolescents.

METHODS: We performed quasi-Poisson regression analyses at 0–4, 5–9, 10–14, and 15–19 years of age using nationwide time-series data from the Republic of Korea (2011–2015). We constructed distributed lag linear models employing a generalized difference-in-differences method and controlling for other air pollutants.

RESULTS: A 10.0-ppb increase in 8-hour maximum ozone levels was associated with a higher risk of hospital admissions due to pneumonia at 0–4 (relative risk [RR] = 1.02, 95% confidence interval [CI]: 1.01, 1.03) and 5–9 years of age (RR = 1.06, 95% CI: 1.04, 1.08) but not at 10–14 (RR = 1.01, 95% CI: 0.98, 1.04) or 15–19 years of age (RR = 1.01, 95% CI: 0.97, 1.06). The association between ozone and hospital admissions due to pneumonia was stronger in cool seasons (from November to April) than in warm seasons (from May to October) but was similar between boys and girls.

CONCLUSIONS: Short-term exposure to ozone was associated with a higher risk of pneumonia at 0–4 and 5–9 years of age but not at 10–14 or 15–19 years of age. Our findings can help identify vulnerable periods, determine the target populations for public health interventions, and establish air pollution standards.

KEY WORDS: Ozone, Pneumonia, Children, Adolescent, Time-series study

INTRODUCTION

Ambient ozone, an air pollutant, is a global public health issue. Ozone has strong oxidative potential and has been associated with various health outcomes, such as airway inflammation [1], decreased lung function [2], hospital admission due to respiratory diseases [3], and mortality [4]. Because ozone is primarily generated from photochemical reactions of other air pollutants under high temperatures and sunlight, its level is predicted to rise globally due to climate change [5].

Previous experimental studies suggest that ozone can increase the susceptibility to respiratory infections, such as pneumonia [6,7]. However, the number of epidemiological studies on the association between ozone and pneumonia is insufficient compared with that of studies investigating the association between other pollutants (e.g., particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ [PM_{2.5}]) and pneumonia, and their results are inconsistent [8–15]. For example, short-term exposure to ozone has been associated with a higher risk of pneumonia in time-series studies conducted in the United States [9] and China [8], while the association was not found in a case-crossover study in the United States [10]. In addition, although previous studies suggest the effect modification by age on the association between ozone and pneumonia [8,9] and consider children and adolescents to be especially susceptible to air pollution [16], evidence for these younger populations is limited [9,11–14].

Therefore, using nationwide time-series data of Korean children and adolescents, we investigated the association between ozone exposure and pneumonia, which represents the most common cause of hospitalization among individuals under 18 years of age [17] and the second most expensive condition for hospitalization among children [18]. Because we hypothesized that the

effect size would be larger among younger than older subjects, we performed analyses stratified by age group and compared the results in each stratum.

MATERIALS AND METHODS

Patient and hospital admission data

We performed a time-series study using data on daily counts of hospital admissions with a principal admission diagnosis of pneumonia (International Classification of Diseases, 10th revision code J12–J18) among children and adolescents (0–19 years of age) between January 1, 2011 and December 31, 2015. We obtained the data from the National Health Insurance Service (NHIS) of the Republic of Korea, which provides universal health coverage to all the residents of Korea [19]. In this study, the NHIS generated and provided data by aggregating the count of only the first day of admission for each hospitalization. The accuracy of diagnosis in the NHIS data has been previously reported to be high, especially for inpatient settings [20–23]. The outcome daily counts were aggregated by region (16 regions constituting the Republic of Korea) (Supplementary Material 1), age group (0–4, 5–9, 10–14, and 15–19 years), and sex, leading to 128 separate time-series data sets.

Air pollution and meteorological data

We estimated 8-hour maximum ozone concentrations (highest 8-hour moving average concentration) and daily mean concentrations of particulate matter with an aerodynamic diameter

101 $\leq 10 \mu\text{m}$ (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) in
102 each region from the 24-hour monitoring data of urban monitoring stations. We obtained this
103 data from the National Ambient Air Monitoring Information System. This national system
104 continuously collects data from 318 fixed-site monitoring stations, located based on the
105 population distribution and operated under strict quality control [24]. We first calculated 8-hour
106 maximum ozone levels and daily mean PM_{10} , NO_2 , SO_2 , and CO levels at each monitoring
107 station after excluding missing values (<5% of total data). We then calculated region-specific
108 values by averaging 8-hour maximum ozone levels and daily mean PM_{10} , NO_2 , SO_2 , and CO
109 levels from all monitoring stations located in each region. Because nationwide monitoring of
110 $\text{PM}_{2.5}$ was not conducted during the study period (2011–2015), we did not consider $\text{PM}_{2.5}$ levels
111 in the present study.

112 We estimated daily mean temperature ($^{\circ}\text{C}$) and relative humidity (%) for each region using 24-
113 hour measurement data from the Korea National Meteorological Administration. If there were
114 more than one weather station in the region, we used averaged temperature and relative humidity
115 values for further analyses.

116

117 **Statistical analysis**

118 We performed quasi-Poisson generalized linear regression analyses to evaluate the short-term
119 effects of 8-hour maximum ozone levels on hospital admissions due to pneumonia. All further
120 analyses were performed using data stratified by the age groups of 0–4, 5–9, 10–14, and 15–19
121 years.

122 To assess the delayed and cumulative effects of lag-day exposures, we constructed distributed lag
123 linear models [25]. In these models, we implemented lag structures up to 7 days with a
124 polynomial function with 4 degrees of freedom (df), according to previous studies investigating
125 the association between short-term exposure to ozone levels and respiratory infection-related
126 outcomes [9,11] and the lag-specific associations between ozone and pneumonia estimated from
127 distributed lag linear models (adjusted for region, day, temperature, relative humidity,
128 population, and other air pollutants) (Supplementary Material 2). We selected the df according to
129 a previous study [26]. However, we also confirmed the robustness of the results in models with
130 different df in sensitivity analyses.

131 To improve causal inference by adjusting for confounders related to spatial units of the analysis
132 (i.e., regions) and those related to temporal units (i.e., days), we employed a generalized
133 difference-in-differences method [27,28], a formal causal modeling approach [27], by
134 introducing dummy variables for spatial units (16 regions) and temporal units (1,826 days) in the
135 time-series analytical models. The common form of the difference-in-differences method
136 leverages two areas (or exposures) and two time points. However, the difference-in-differences
137 method can be applied to data with multiple spatial and temporal units by examining the
138 association between exposure and outcome of interest (both measured at the level of a predefined
139 spatial and temporal unit) adjusted for spatial and temporal units [29,30]; therefore, in the
140 context of short-term air pollution epidemiology, it can be applied as a multi-region time-series
141 study adjusted for spatial (e.g., regions) and temporal units (e.g., days). This method can control
142 both measured confounders and unmeasured ones, such as sociodemographic factors [27,28].
143 Therefore, although this method is computationally demanding, it has an edge over other causal

inference methods, such as those using a propensity score, which can only control measured confounders.

We also adjusted for daily mean temperature and relative humidity up to 7 days, all of which were modeled with a 3-df natural cubic spline according to previous studies [8,11], and log-transformed population of each region as an offset. Finally, to confirm that the results were not confounded by other air pollutants, we further adjusted the analyses for daily mean PM₁₀, NO₂, SO₂, and CO levels up to 7 days. Therefore, the main analytical models from which we extracted the main findings can be summarized as follows:

$$\log[E(Y_{s,t})] = \beta_0 + \beta_1 \text{Ozone}_{s,t} + \beta_2 D_s + \beta_3 D_t + \beta_4 \text{Temp}_{s,t} + \beta_5 \text{Humi}_{s,t} + \beta_6 \text{Pollut}_{s,t} + \log(\text{Pop}_{s,t})$$

where $Y_{s,t}$ is the number of hospital admissions due to pneumonia in region 's' at day 't.'

$\text{Ozone}_{s,t}$, $\text{Temp}_{s,t}$, $\text{Humi}_{s,t}$, and $\text{Pollut}_{s,t}$ are the cross-basis matrices of ozone, temperature, relative humidity, and other air pollutants (PM₁₀, NO₂, SO₂, and CO), respectively, in region 's' at day 't' with aforementioned lag structures and concentration-response curves. D_s and D_t are dummy variables for regions and days, respectively. $\text{Pop}_{s,t}$ is the population of region 's' in the year of day 't.' All variation inflation factors estimated from quasi-Poisson regression models including terms for daily 8-hour maximum ozone levels and daily mean levels of PM₁₀, NO₂, SO₂, CO, temperature, and relative humidity were lower than 4.0 at 0–4, 5–9, 10–14, and 15–19 years of age. In addition, the shapes of the concentration-response curves for the associations between ozone and pneumonia at 0–4, 5–9, 10–14, and 15–19 years of age were investigated using the distributed lag non-linear models adjusted for the same covariates (the concentration-response curves were modeled with a natural cubic spline with 3 df).

165 Because several studies suggest heterogeneity of the association between ozone levels and
166 pneumonia by seasons [8,10], we stratified the analyses by warm seasons (from May to October)
167 and cool seasons (from November to April). We also performed sex-stratified analyses to assess
168 the associations' similarity between boys and girls.

169 We conducted the following sensitivity analyses: First, we repeated the analyses after excluding
170 the region with the lowest ozone levels (Seoul, 28.1 ppb) and the one with the highest levels
171 (Jeju-do, 41.6 ppb), to verify possible violations of the positivity assumption [31]. The positivity
172 assumption is essential in a causal inference that each exposure level (or intervention and
173 control) could be observable at each observation. In this study, it was likely that some ozone
174 levels would not be observed in the regions with the highest and lowest ozone levels, in which
175 case there was a concern that causal inference could not be adequately made in these regions.
176 Second, according to previous studies [9–12], we further adjusted for the influenza epidemics,
177 defined as the daily number of hospital admissions due to influenza of more than 80 cases in
178 each region (1.0% of the study period). Third, we used different df for the lag structures (2 to 5
179 df) and concentration-response curves (2 to 5 df) in the distributed lag linear models. Fourth, we
180 conducted conventional two-stage time-series analyses to confirm the robustness of the results.
181 In these analyses, we first obtained region-specific associations between ozone levels and
182 pneumonia adjusted for calendar time (natural cubic spline, 8 df per year), daily mean
183 temperature and relative humidity up to 7 days (cross-basis matrices, 3 df), and other pollutants
184 (PM₁₀, NO₂, SO₂, and CO) up to 7 days (cross-basis matrices). We then pooled the region-
185 specific results by performing meta-analyses.

186 We conducted the analyses using R version 4.0.3 (R Foundation for Statistical Computing,
187 Vienna, Austria).

188

189 **Ethics statement**

190 Because we used secondary count data de-identified by the NHIS, the need for written informed
191 consent was waived. The Ethics Review Board of Seoul National University Hospital approved
192 the study protocol (approval number E-1909-096-1065), and we performed the study according
193 to the tenets of the Declaration of Helsinki.

194

195 **RESULTS**

196 The mean ($\pm$ standard deviation) daily counts of hospital admissions due to pneumonia during
197 the study period (2011–2015) were 493 ($\pm$ 276) at 0–4 years of age, 100 ($\pm$ 90) at 5–9 years of
198 age, 29 ($\pm$ 26) at 10–14 years of age, and 12 ($\pm$ 10) at 15–19 years of age (Table 1). The daily
199 counts of hospital admissions due to pneumonia were higher in cool than in warm seasons
200 (Supplementary Material 3). The mean 7-day moving average of the daily 8-hour maximum
201 ozone levels during the study period was 37.2 ppb, which was comparable to the levels in the
202 United States and other developed countries [32] (Table 1). The ozone levels were higher in
203 warm than in cool seasons, while PM₁₀, NO₂, SO₂, and CO levels were higher in cool than in
204 warm seasons (Supplementary Material 3).

205 The correlations of ozone levels with other air pollutant levels and meteorological factors were

206 weak, with the absolute values of Spearman's correlation coefficients less than 0.30, except for
207 the correlation between ozone levels and temperature ($r = 0.43$, p -value < 0.0001)
208 (Supplementary Material 4).

209 After visual inspection of the concentration-response curves for the associations between ozone
210 levels and pneumonia (Figure 1), we estimated the delayed and cumulative effects of ozone
211 levels up to 7 days on pneumonia using the distributed lag linear models. A 10.0-ppb increase in
212 ozone levels was associated with a higher risk of pneumonia at 0–4 (relative risk [RR] = 1.02,
213 95% confidence interval [CI]: 1.01, 1.03) and 5–9 years of age (RR = 1.06, 95% CI: 1.04, 1.08),
214 but not at 10–14 (RR = 1.01, 95% CI: 0.98, 1.04) or 15–19 years of age (RR = 1.01, 95% CI:
215 0.97, 1.06) (Table 2).

216 Using the same analytical models, we also found positive associations of a 10.0- $\mu\text{g}/\text{m}^3$ increase
217 in PM_{10} (RR = 1.01, 95% CI: 1.00, 1.02) and a 1.0-ppb increase in SO_2 (RR = 1.01, 95% CI:
218 1.00, 1.01) with pneumonia at 0–4 years of age; however, in other age groups, the associations
219 between air pollutant levels and pneumonia were generally null or inverse, except for the
220 association with CO (Supplementary Material 5).

221 When we stratified the analyses by season, the association between ozone and pneumonia was
222 stronger in cool seasons (from November to April) than in warm seasons (from May to October)
223 (Table 3). However, we found no appreciable sex-differences in the association between ozone
224 and pneumonia (Supplementary Material 6).

225 We explored the sensitivity of the analyses by using alternative data and covariate selections and
226 model specifications. First, the results were insensitive to the exclusion of the region with the

lowest ozone levels (Supplementary Material 7) and the region with the highest ozone levels (Supplementary Material 8). Second, after further adjusting for the influenza epidemics, the results did not change appreciably (Supplementary Material 9). Third, we found robust results using different df for the lag structures and concentration-response curves (data not shown). Fourth, the results were consistent between conventional two-stage time-series analyses and the analyses applying the difference-in-differences method, except that the association at 5–9 years of age was only found in the difference-in-differences approach. This heterogeneity might be due to strict control of potential confounder (related to spatial and temporal units) by the difference-in-differences method (Supplementary Material 10).

236

237 **DISCUSSION**

The ozone levels in the Republic of Korea, as presented in this study, were comparable to those in the United States and other developed countries. We found that ozone levels were associated with a higher risk of hospital admissions due to pneumonia at 0–4 and 5–9 years of age, but not at 10–14 or 15–19 years of age, in the formal causal inference models. Because the socioeconomic burden of pneumonia in children and adolescents is high [17,18] and air pollution may increase the associated costs [33], the results of the present study have substantial public health implications.

Previous studies exploring the association between ozone exposure and pneumonia among children and adolescents are relatively rare and have yielded heterogeneous results [12]. For example, a time-series study conducted in 17 states of the United States reported a positive

248 association between ozone levels and emergency department visits due to pneumonia at 0–18
249 years of age [9], while another time-series study in Hanoi, Vietnam did not find an association
250 between ozone levels and hospital admissions due to pneumonia at 0–17 years of age [11].
251 Furthermore, few studies have identified high-risk age groups by stratifying children and
252 adolescents by age: Some studies suggested that associations between ozone and pneumonia
253 would be more prominent at 0–4 years of age than at older ages [13,14]. However, another time-
254 series study failed to identify an association between ozone and pneumonia at 0–1 and 1–5 years
255 of age [11]. For older children and adolescents, a case-crossover study in California found no
256 association between ozone and emergency department visits due to pneumonia at 5–18 years of
257 age [13]. Such observed heterogeneity may be attributable to differences in population
258 characteristics (related, for example, to sensitivity and adaptive capacity), exposure levels,
259 measurement error for exposure and outcome, and analytical strategies (e.g., study design,
260 statistical models, and methods used to control for the confounding effects of various factors,
261 including other air pollutants).

262 In the generalized difference-in-differences analyses, considering the effects of other air
263 pollutants, we found an association between ozone levels and pneumonia at 0–4 and 5–9 years of
264 age but not at 10–14 or 15–19 years of age. It has been suggested that ozone exposure can
265 increase the risk of airway infections by affecting host immunity [34,35]. Thus, the immature
266 immune system of younger children may be responsible for these findings [36]. The results
267 might also reflect lower rates of outdoor activity (and time spent outdoors) among middle and
268 high school students compared with those of younger children in the Republic of Korea [37],
269 given that indoor ozone levels are generally lower than outdoor levels [15].

270 Most previous studies [8,10,11,13,15], but not all of them [14], have reported a stronger
271 association between ozone and pneumonia in warm than in cool seasons. These findings are
272 inconsistent with the results of this study, which showed a stronger association in cool seasons.
273 The reason for this inconsistency is not clear. However, although ambient ozone levels are lower
274 in cool seasons, outdoor activities are likely to increase on sunny days with higher temperatures
275 (possibly days with higher ozone levels as well) in cool seasons but decrease on similar days in
276 warm seasons, resulting in different individual exposure patterns according to seasons [14]. In
277 addition, air conditioning with low ventilation due to closed windows in warm seasons
278 (especially on sunny days with higher temperature) can also prevent the penetration of outdoor
279 ozone, hence reducing exposure [15]. Finally, the observed stronger association between ozone
280 and pneumonia in cool seasons might be affected by seasonal differences in ozone levels and
281 their variance (Supplementary Material 3) or the unmeasured confounding effect of seasonal
282 variations in infections. However, we found robust results in analyses further adjusted for
283 influenza epidemics.

284 This study has limitations. First, we used monitoring data for ozone levels from fixed sites as a
285 proxy for population exposure. Although this exposure assignment method is widely used in air
286 pollution epidemiology studies (especially those exploring the effects of short-term exposure to
287 air pollution) and ozone levels are spatially homogenous compared with the levels of other air
288 pollutants [38], it reportedly produces the Berkson-type measurement error, leading to lower
289 precision rather than to bias [39]. Second, there exists a concern of outcome misclassification.
290 However, because we defined the outcome based on the principal diagnosis of hospital
291 admission due to pneumonia determined by a physician, problems related to the precision of the

292 diagnosis can be assumed to be low. In contrast, as we only analyzed relatively severe cases
293 leading to hospital admission, the possibility that the association between ozone and pneumonia
294 would be attenuated after including relatively mild cases remains. Third, although negative
295 control outcomes can be used to detect bias and strengthen causal inference in the observational
296 study design [40], we could not apply them (e.g., hospital admissions due to appendicitis) in the
297 present study, due to the lack of sufficient information. Fourth, this study used all hospitalization
298 cases, rather than hospitalization only through the emergency room, as an outcome; therefore, a
299 considerable proportion of hospitalization might be scheduled ones and not associated with
300 ozone exposure, leading the results toward the null hypothesis.

301 However, the present study has strengths that merit highlighting. First, this is one of a few
302 studies that systematically evaluated the susceptible periods to ozone exposure regarding
303 pneumonia among children and adolescents, who are considered vulnerable populations.
304 Therefore, this study can provide valuable evidence to select priority target populations for
305 public health interventions and policies. Second, because the present study included all cases of
306 hospital admissions due to pneumonia among children and adolescents in the Republic of Korea
307 during the study period (2011–2015), the possibility of selection bias is low. Third, to the best of
308 our knowledge, this is the first study applying a formal causal inference method to investigate the
309 effect of ozone levels on pneumonia. Using a generalized difference-in-differences method, we
310 could control for a wide range of confounders related to the spatial and temporal units of the
311 study, thus substantially improving causal inference. Fourth, we assessed the independent effect
312 of ozone on pneumonia by considering other air pollutants that can act as confounders. These
313 analyses not only provide stronger evidence for a causal relationship, but also have direct public

314 health implications, by aiding the formulation of air pollution standards for a specific air
315 pollutant.

316 In conclusion, ozone levels were associated with a higher risk of pneumonia at 0–4 and 5–9
317 years of age, but not at 10–14 or 15–19 years of age. This study provides valuable insights to
318 help identify vulnerable periods to ozone exposure in terms of pneumonia, determine the target
319 populations for public health interventions and policies, and establish air pollution standards
320 (considering the observed association between ozone and pneumonia below the current ozone
321 standards). However, because the results of the present study might also reflect different outdoor
322 activity patterns by age groups as well as vulnerability, future studies involving a more precise
323 estimation of ozone exposures by considering behavioral factors are needed.

324

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Table 1. Daily hospital admissions due to pneumonia, air pollution, and meteorological factors in Korea, 2011–2015

	Mean (SD)	Percentile					IQR
		Min	25th	50th	75th	Max	
Daily counts of hospital admissions due to pneumonia							
0–4 years	493 (276)	88	295	424	633	2,507	338
5–9 years	100 (90)	6	46	70	114	726	68
10–14 years	29 (26)	0	12	21	35	274	23
15–19 years	12 (10)	0	6	10	15	117	9
Air pollution levels							
Ozone ^a (ppb)	37.3 (13.4)	6.8	26.8	36.5	46.7	90.3	19.9
PM ₁₀ ^b (µg/m ³)	46.4 (17.4)	11.6	34.4	43.6	54.9	203.0	20.6
NO ₂ ^b (ppb)	20.7 (8.9)	2.5	14.2	19.2	25.7	63.3	11.6
SO ₂ ^b (ppb)	4.8 (2.0)	1.0	3.3	4.6	6.0	17.3	2.6
CO ^b (ppb)	496.0 (150.3)	172.3	394.9	469.9	568.8	1,502.0	173.9
Meteorological factors ^c							
Temperature (°C)	13.2 (9.8)	-14.6	4.8	14.4	21.7	33.1	16.9
Relative humidity (%)	67.0 (15.2)	11.3	56.8	68.5	78.3	99.9	21.5

Abbreviations: SD, standard deviation; IQR, interquartile range

^aDistribution of 7-day moving averages of daily 8-hour maximum concentrations during the study period (2011–2015).

448 ^bDistribution of 7-day moving averages of daily mean concentrations during the study period
449 (2011–2015).

450 ^cDistribution of daily averages during the study period (2011–2015).

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452 **Table 2.** Cumulative effects of ozone levels up to 7 days on pneumonia^a, stratified by age group

	Not adjusted for other air pollutants ^b		Adjusted for other air pollutants ^b	
	RR	95% CI	RR	95% CI
0–4 years	1.02	(1.01, 1.03)	1.02	(1.01, 1.03)
5–9 years	1.06	(1.04, 1.08)	1.06	(1.04, 1.08)
10–14 years	1.02	(0.99, 1.05)	1.01	(0.98, 1.04)
15–19 years	1.01	(0.97, 1.06)	1.01	(0.97, 1.06)

453 Abbreviations: RR, relative risk; CI, confidence interval

454 ^aCumulative effects were estimated for a 10.0-ppb increase in ozone levels, after adjustment for
 455 region, day, temperature, relative humidity, and population (and PM₁₀, NO₂, SO₂, and CO in
 456 models further adjusted for other air pollutants).

457 ^bPM₁₀, NO₂, SO₂, and CO.

458

459 **Table 3.** Cumulative effects of ozone levels up to 7 days on pneumonia^a, by age and season

	Warm season (from May to October)		Cool season (from November to April)		서식 있는 표
	RR	95% CI	RR	95% CI	
0–4 years	1.01	(0.99, 1.02)	1.06	(1.04, 1.09)	
5–9 years	1.05	(1.02, 1.07)	1.07	(1.03, 1.12)	
10–14 years	1.03	(0.99, 1.07)	0.95	(0.88, 1.02)	
15–19 years	1.01	(0.96, 1.07)	1.09	(0.98, 1.20)	

460 Abbreviations: RR, relative risk; CI, confidence interval

461 ^aCumulative effects were estimated for a 10.0-ppb increase in ozone levels, after adjustment for
462 region, day, temperature, relative humidity, population, and other air pollutants (PM₁₀, NO₂, SO₂,
463 and CO).

464

465 **Figure legend**

466 **Figure 1.** Concentration-response curves for the associations between ozone and pneumonia by
467 age group, estimated from the distributed lag non-linear models adjusted for region, day,
468 temperature, relative humidity, population, and other air pollutants (PM₁₀, NO₂, SO₂, and CO).

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Age-specific effects of ozone on pneumonia in Korean children and adolescents: ~~a~~A nationwide time-series study

Manuscript category: Original article

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32

33 **Running title:** Ozone and pneumonia in children and adolescents

34

Abstract

OBJECTIVES: ~~To~~ The aim of this study was to estimate the age-specific effects of 8-hour maximum ozone levels on pneumonia in children and adolescents.

METHODS: We performed quasi-Poisson regression analyses ~~at for individuals of~~ 0–4, 5–9, 10–14, and 15–19 years of age using nationwide time-series data from the Republic of Korea (2011–2015). We constructed distributed lag ~~non~~-linear models employing a generalized difference-in-differences method and controlling for other air pollutants.

RESULTS: ~~Compared with ozone levels of 40.0 ppb, the risk of hospital admissions due to pneumonia increased for ozone levels of 60.0. A 10.0-ppb increase in 8-hour maximum ozone levels was associated with a higher risk of hospital admissions due to pneumonia, and 70.0 ppb~~ at 0–4 (relative risk [RR] = 1.052, 95% confidence interval [CI]: 1.021–1.073 for ozone levels of 60.0 ppb; RR = 1.06, 95% CI: 1.02, 1.09 for 70.0 ppb) and 5–9 years of age (RR = 1.1306, 95% CI: 1.084–1.178 for 60.0 ppb; RR = 1.16, 95% CI: 1.09, 1.24 for 70.0 ppb), but not at 10–14 (RR = 1.01, 95% CI: 0.98–1.04) or 15–19 years of age (RR = 1.01, 95% CI: 0.97–1.056). We also observed an increased risk of hospital admissions due to pneumonia only among children aged 0–4 and 5–9 years, for ozone levels as low as 30.0 ppb (reference: 20.0 ppb) and in analyses assuming linear concentration-response curves. The association between ozone and hospital admissions due to pneumonia was stronger ~~was stronger~~ in cool seasons (from November to April) than in warm seasons (from May to October), but was similar between boys and girls.

CONCLUSIONS: Short-term exposure to ozone was associated with a higher risk of pneumonia

56 at 0–4 and 5–9 years of age, but not at 10–14 or 15–19 years of age. Our findings can help
57 identify vulnerable periods, determine the target populations for public health interventions, and
58 establish air pollution standards.

59 **KEY WORDS:** Ozone, Pneumonia, Children, Adolescent, Time-series study

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INTRODUCTION

Ambient ozone, an air pollutant, is a global public health issue. Ozone has strong oxidative potential and has been associated with various health outcomes, such as airway inflammation [1], decreased lung function [2], hospital admission due to respiratory diseases [3], and mortality [4]. Because ozone is primarily generated from photochemical reactions of other air pollutants under high temperatures and sunlight, ~~its ozone~~ levels ~~is-are~~ predicted to rise globally due to climate change [5].

Previous experimental studies ~~have~~ suggested ~~ed~~ that ozone can increase the susceptibility to respiratory infections, such as pneumonia [6,7]. However, the number of epidemiological studies on the association between ozone and pneumonia is insufficient compared with that of studies investigating the association between other pollutants (e.g., particulate matter with an aerodynamic diameter ≤ 2.5 μm [PM_{2.5}]) and pneumonia, and their results are inconsistent [8–15]. For example, short-term exposure to ozone has been associated with a higher risk of pneumonia in time-series studies conducted in the United States [9] and China [8], while ~~the-an~~ association was not found in a case-crossover study in the United States [10]. In addition, although previous studies ~~have~~ suggested ~~that~~ ~~there may be an~~ effect modification by age on the association between ozone and pneumonia [8,9], and ~~consider-that~~ children and adolescents ~~to-~~ ~~may~~ be especially susceptible to air pollution [16], evidence for these younger populations is limited [9,11–14].

Therefore, using nationwide time-series data of Korean children and adolescents, we investigated the association between ozone exposure and pneumonia, which represents the most common

cause of hospitalization among individuals under 18 years of age [17] and the second most expensive condition for hospitalization among children [18]. ~~Because we~~We hypothesized that the effect size would be larger among younger than older subjects, ~~and~~ we ~~therefore~~ performed analyses stratified by age group and compared the results in each stratum.

MATERIALS AND METHODS

Patient and hospital admission data

We performed a time-series study using data on daily counts of hospital admissions with a principal admission diagnosis of pneumonia (International Classification of Diseases, 10th revision code J12–J18) among children and adolescents (0–19 years of age) between January 1, 2011 and December 31, 2015. We obtained ~~the~~ data from the National Health Insurance Service (NHIS) of the Republic of Korea, which provides universal health coverage to all ~~the~~ residents of Korea [19]. In this study, the NHIS generated and provided data by aggregating the count of only the first day of admission for each hospitalization. The accuracy of diagnoses in the NHIS data has been previously reported to be high, especially for inpatient settings [20–23]. The outcome daily counts were aggregated by region (16 regions constituting the Republic of Korea) (Supplementary Material 1), age group (0–4, 5–9, 10–14, and 15–19 years), and sex, leading to 128 separate time-series data sets.

Air pollution and meteorological data

We estimated 8-hour maximum ozone concentrations (highest 8-hour moving average concentration) and daily mean concentrations of particulate matter with an aerodynamic diameter $\leq 10 \mu\text{m}$ (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) in each region from the 24-hour monitoring data of urban monitoring stations. We obtained this data from the National Ambient Air Monitoring Information System. This national system continuously collects data from 318 fixed-site monitoring stations, which are located based on the population distribution and operated under strict quality control [24]. We first calculated 8-hour maximum ozone levels and daily mean PM_{10} , NO_2 , SO_2 , and CO levels at each monitoring station after excluding missing values (<5% of total data). We then calculated region-specific values by averaging 8-hour maximum ozone levels and daily mean PM_{10} , NO_2 , SO_2 , and CO levels from all monitoring stations located in each region. Because nationwide monitoring of $\text{PM}_{2.5}$ was not conducted during the study period (2011–2015), we did not consider $\text{PM}_{2.5}$ levels in the present study.

We estimated daily mean temperature ($^{\circ}\text{C}$) and relative humidity (%) for each region using 24-hour measurement data from the Korea National Meteorological Administration. If there were more than one multiple weather stations in the a region, we used averaged temperature and relative humidity values for further analyses.

Statistical analysis

We performed quasi-Poisson generalized linear regression analyses to evaluate the short-term effects of 8-hour maximum ozone levels on hospital admissions due to pneumonia. All further

analyses were performed using data stratified by the age groups of 0–4, 5–9, 10–14, and 15–19 years.

To assess the delayed and cumulative effects of lag-day exposures ~~using potentially non-linear concentration-response curves~~, we constructed distributed lag ~~non~~-linear models [25]. In these models, we implemented lag structures up to 7 days with a polynomial function with 4 degrees of freedom (df), according to previous studies investigating the association between short-term exposure to ozone levels and respiratory infection-related outcomes [9,11] and the lag-specific associations between ozone and pneumonia estimated from distributed lag linear models (adjusted for region, day, temperature, relative humidity, population, and other air pollutants) (Supplementary Material 2), ~~with a polynomial function with 4 degrees of freedom (df) and concentration-response curves with a natural cubic spline with 3 df~~. We selected the df- degrees of freedom according to a previous study [26]. However, we also confirmed the robustness of the results in models with different df- degrees of freedom in sensitivity analyses. ~~We set 8-hour maximum ozone levels of 40.0 ppb as a reference (close to the mean of 8-hour maximum ozone levels of 37.2 ppb in the Republic of Korea during the study period) and presented the results for 60.0 ppb (suggested ozone standard by Clean Air Scientific Advisory Committee) [27] and 70.0 ppb (current ozone standard by the National Ambient Air Quality Standards) [28].~~

To improve causal inference by adjusting for confounders related to spatial units of the analysis (i.e., regions) and those related to temporal units (i.e., days), we employed a generalized difference-in-differences method [27,28], a formal causal modeling approach [27], by

introducing dummy variables for spatial units (16 regions) and temporal units (1,826 days) in the time-series analytical models. The common form of the difference-in-differences method leverages two areas (or exposures) and two time points. However, the difference-in-differences method can be applied to data with generalized to multiple spatial and temporal units by examining the association between the exposure and outcome of interest (both are measured at the level of a predefined spatial and temporal unit) after being adjusted for spatial and temporal units [29,30]. ~~(reference).~~ Therefore, in the context of short-term air pollution epidemiology, it can be applied as this method can be applied as a multi-region time-series study on the association between air pollution and outcome of interest, adjusted for in which both spatial (e.g., regions) and temporal units (e.g., days) are adjusted for. This method can control for ~~for~~ both measured and unmeasured confounders ~~and unmeasured ones~~, such as sociodemographic factors [27,28]. Therefore, although this method is computationally demanding, it has an edge over other causal inference methods, such as those using a propensity score, which can only control for measured confounders.

We also adjusted for daily mean temperature and relative humidity up to 7 days, all of which were modeled with a ~~3-df~~ natural cubic spline with 3 degrees of freedom according to previous studies [8,11], and the log-transformed population of each region as an offset. Finally, to confirm that the results were not confounded by other air pollutants, we further adjusted the analyses for daily mean PM₁₀, NO₂, SO₂, and CO levels up to 7 days. ~~Details of the main analytical models (distributed lag non-linear models) from which we extracted the main findings are presented in the Supplementary Material 2.~~ Therefore, the main analytical models from which we extracted the main findings can be summarized as follows:

서식 있음: 강조

$$\log[E(Y_{s,t})] = \beta_0 + \beta_1 \text{Ozone}_{s,t} + \beta_2 D_s + \beta_3 D_t + \beta_4 \text{Temp}_{s,t} + \beta_5 \text{Humi}_{s,t} + \beta_6 \text{Pollut}_{s,t} + \log(\text{Pop}_{s,t})$$

where $Y_{s,t}$ is the number of hospital admissions due to pneumonia in region s on day t ; $\text{Ozone}_{s,t}$, $\text{Temp}_{s,t}$, $\text{Humi}_{s,t}$, and $\text{Pollut}_{s,t}$ are the cross-basis matrices of ozone, temperature, relative humidity, and other air pollutants (PM_{10} , NO_2 , SO_2 , and CO), respectively, in region s on day t with the aforementioned lag structures and concentration-response curves; D_s and D_t are dummy variables for regions and days, respectively; and $\text{Pop}_{s,t}$ is the population of region s in the year of day t . All variation in inflation factors estimated from quasi-Poisson regression models including terms for daily 8-hour maximum ozone levels and daily mean levels of PM_{10} , NO_2 , SO_2 , CO , temperature, and relative humidity were lower than 4.0 in the age groups of 0–4, 5–9, 10–14, and 15–19 years of age. In addition, the shapes of the concentration-response curves for the associations between ozone and pneumonia at 0–4, 5–9, 10–14, and 15–19 years of age were investigated using the distributed lag non-linear models adjusted for the same covariates (the concentration-response curves were modeled with a natural cubic spline with 3 degrees of freedom).

Additionally, we constructed distributed lag linear models to estimate the effects of 8-hour maximum ozone levels (in 10.0 ppb increments) on hospital admissions due to pneumonia, assuming linear associations. These models were adjusted for the same covariates listed above (region, day, temperature, relative humidity, other air pollutants, and population).

To assess the combined effects of co-exposure to ozone and other air pollutants (PM_{10} , NO_2 , SO_2 , and CO) on pneumonia, we performed a weighted quantile sum regression analysis [29]. This method, which combines multiple correlated exposures into a weighted quantile sum index,

is accurate and effective in dealing with high dimensionality and multicollinearity problems [29]. In this analysis, we considered exposures to ozone and other air pollutants with lag day 0 to 7 (i.e., a total of 40 exposures) as exposures of interest and calculated the weighted quantile sum index by multiplying the quartiles of each exposure and their corresponding weights estimated from the magnitude of individual effects, which were constrained between 0 and 1, and summed to 1. Then, we explored the association between the weighted quantile sum index and pneumonia adjusted for daily mean temperature and relative humidity, all of which were modeled with a natural cubic spline with 3 df, and the regions. We determined a quasi-Poisson distribution as the outcome distribution and set the ratio of training to validation data as 6:4. We obtained the results with 100 bootstrap samples. Details of the weighted quantile sum regression models are presented in the Supplementary Material 3.

Because several studies have suggested heterogeneity of the association between ozone levels and pneumonia by seasons [8,10], we stratified the analyses by according to warm seasons (from May to October) and cool seasons (from November to April). We also performed sex-stratified analyses to assess the associations' similarity between boys and girls.

We conducted the following sensitivity analyses: First, we estimated the effects of 8-hour maximum ozone levels on pneumonia for 30.0, 50.0, and 70.0 ppb (instead of 60.0 and 70.0 ppb) with a reference of 20.0 ppb (instead of 40.0 ppb) because previous studies conducted among children suggested thresholds of 8-hour maximum ozone levels between 20.0 ppb and 30.0 ppb for some respiratory outcomes, such as asthma [30,31], or reported an association between 8-hour maximum ozone levels and pneumonia down to 20.0 ppb [14]. Second, First, we repeated the

208 analyses after excluding the region with the lowest ozone levels (Seoul, 28.1 ppb) and the one
 209 with the highest levels (Jeju-do Province, 41.6 ppb), to verify possible violations of the positivity
 210 assumption [31]. The positivity assumption, which is essential in a for causal inference,
 211 postulates that each exposure level (or intervention and control) could be observable at each
 212 observation. In this study, it was likely that some ozone levels would not be observed in the
 213 regions with the highest and lowest ozone levels, in which case there was a concern that causal
 214 inference could not be adequately made in these regions. ~~Third~~Second, according to previous
 215 studies [9–12], we further adjusted for ~~the~~ influenza epidemics, defined as ~~the a~~ daily number of
 216 hospital admissions due to influenza of more than 80 cases in each region (1.0% of the study
 217 period). ~~Fourth~~Third, we used different ~~df~~ degrees of freedom for the lag structures (2 to 5
 218 ~~df~~degrees of freedom) and concentration-response curves (2 to 5 ~~df~~degrees of freedom) in the
 219 distributed lag ~~non~~-linear models. Fourth, we conducted conventional two-stage time-series
 220 analyses to confirm the robustness of the results. In these analyses, we first obtained region-
 221 specific associations between ozone levels and pneumonia adjusted for calendar time (natural
 222 cubic spline, 8-~~df~~ degrees of freedom per year), daily mean temperature and relative humidity
 223 up to 7 days (cross-basis matrices, 3 ~~df~~degrees of freedom), and other pollutants (PM₁₀, NO₂, SO₂,
 224 and CO) up to 7 days (cross-basis matrices). We then pooled the region-specific results by
 225 performing meta-analyses.

226 We conducted the analyses using R version 4.0.3 (R Foundation for Statistical Computing,
 227 Vienna, Austria).

228

메모 포함[C1]: As a minor note, “-do” was translated
 here to improve comprehensibility for international
 readers, but if you strongly prefer “-do”, it would not
 be a major problem to revise back.

229 **Ethics statement**

230 Because we used secondary count data de-identified by the NHIS, the need for written informed
231 consent was waived. The Ethics Review Board of Seoul National University Hospital approved
232 the study protocol (approval number E-1909-096-1065), and we performed the study according
233 to the tenets of the Declaration of Helsinki.

234

235 **RESULTS**

236 The mean ($\pm$ standard deviation) daily counts of hospital admissions due to pneumonia during
237 the study period (2011–2015) were 493 ($\pm$ 276) at 0–4 years of age, 100 ($\pm$ 90) at 5–9 years of
238 age, 29 ($\pm$ 26) at 10–14 years of age, and 12 ($\pm$ 10) at 15–19 years of age (Table 1). The daily
239 counts of hospital admissions due to pneumonia were higher in cool than in warm seasons
240 (Supplementary Material 423). The mean 7-day moving average of the daily 8-hour maximum
241 ozone levels during the study period was 37.2 ppb, which ~~was~~is comparable to the levels in the
242 United States and other developed countries [32] (Table 1). The ozone levels were higher in
243 warm than in cool seasons, while PM₁₀, NO₂, SO₂, and CO levels were higher in cool than in
244 warm seasons (Supplementary Material 423).

245 The correlations of ozone levels with other air pollutant levels and meteorological factors were
246 weak, with the absolute values of Spearman's correlation coefficients less than 0.30, except for
247 the correlation between ozone levels and temperature ($r = -0.43$, ~~p~~ P -value < 0.0001)
248 (Supplementary Material 534).

메모 포함[C2]: Spearman correlation coefficients are often denoted with the Greek letter rho (ρ), not "r", which is often used for Pearson correlation coefficients - would this be possible to double-check?

After a visual inspection of the concentration-response curves for the associations between ozone levels and pneumonia (Figure 1), we estimated the delayed and cumulative effects of ozone levels up to 7 days on pneumonia using the distributed lag non-linear models. Compared with ozone levels of 40.0 ppb, ozone levels of 60.0 and 70.0 ppb A 10.0-ppb increase in ozone levels were associated with a higher risk of pneumonia at 0–4 (relative risk [RR] = 1.052, 95% confidence interval [CI]: 1.021, 1.083 for ozone levels of 60.0 ppb; RR = 1.06, 95% CI: 1.02, 1.09 for 70.0 ppb) and 5–9 years of age (RR = 1.1306, 95% CI: 1.084, 1.178 for 60.0 ppb; RR = 1.16, 95% CI: 1.09, 1.24 for 70.0 ppb), but not at 10–14 (RR = 1.071, 95% CI: 0.98, 1.1504 for 60.0 ppb; RR = 1.03, 95% CI: 0.92, 1.15 for 70.0 ppb) or 15–19 years of age (RR = 0.981.01, 95% CI: 0.897, 1.1006 for 60.0 ppb; RR = 0.98, 95% CI: 0.84, 1.15 for 70.0 ppb) (Table 2).

In distributed lag linear models, we found associations between a 10.0-ppb increase in ozone levels and pneumonia at 0–4 (RR = 1.02, 95% CI: 1.01, 1.03) and 5–9 years of age (RR = 1.06, 95% CI: 1.04, 1.08), but not at 10–14 (RR = 1.01, 95% CI: 0.98, 1.04) or 15–19 years of age (RR = 1.01, 95% CI: 0.97, 1.06), consistent with the results of the main distributed lag non-linear models. Using the same analytical models, we also found positive associations of a 10.0- $\mu\text{g}/\text{m}^3$ increase in PM_{10} (RR = 1.01, 95% CI: 1.00, 1.02) and a 1.0-ppb increase in SO_2 (RR = 1.01, 95% CI: 1.00, 1.01) with pneumonia at 0–4 years of age; however, in other age groups, the associations between air pollutant levels and pneumonia were generally null or inverse, except for the association with CO (Supplementary Material 645).

In weighted quantile sum regression analyses, we found that a one-unit increase in weighted

quantile sum indices (a one quantile increase in air pollution mixtures) was associated with a 63% higher risk of pneumonia at 0–4 years of age (95% CI: 1.60, 1.66), 66% at 5–9 years of age (95% CI: 1.61, 1.71), 61% at 10–14 years of age (95% CI: 1.56, 1.67), and 66% at 15–19 years of age (95% CI: 1.60, 1.73).

When we stratified the analyses by season, the association between ozone and pneumonia was stronger in cool seasons (from November to April) than in warm seasons (from May to October) (Table 3). However, we found no appreciable sex differences in the association between ozone and pneumonia (Supplementary Material 756).

We explored the sensitivity of the analyses conducted sensitivity analyses by using alternative ozone cutoffs, data, and covariate selections, and model specifications. First, we found consistent results for the association between 8-hour maximum ozone levels of 30.0, 50.0, and 70.0 ppb and pneumonia with a reference of 20.0 ppb at 0–4 and 5–9 years of age, but not at 10–14 or 15–19 years of age (Supplementary Material 8). Second, the results were insensitive to the exclusion of the region with the lowest ozone levels (Supplementary Material 967) and the region with the highest ozone levels (Supplementary Material 1078). Third, after further adjusting for the influenza epidemics, the results did not change appreciably (Supplementary Material 1189). Fourth, we found robust results using different degrees of freedom for the lag structures and concentration-response curves (data not shown). Fourth, the results were consistent between conventional two-stage time-series analyses and the analyses applying the difference-in-differences method, except that the association at 5–9 years of age was only found in the difference-in-differences approach. This heterogeneity might be due to strict control for

potential confounders (related to spatial and temporal units) by the difference-in-differences method (Supplementary Material 10).

DISCUSSION

The ozone levels in the Republic of Korea, as presented in this study, were comparable to those in the United States and other developed countries. We found that ozone levels were associated with a higher ~~Compared with ozone levels of 40.0 ppb, the~~ risk of hospital admissions due to pneumonia ~~increased for ozone levels of 60.0 and 70.0 ppb~~ at 0–4 and 5–9 years of age, but not at 10–14 or 15–19 years of age, in the formal causal inference models. Because the socioeconomic burden of pneumonia in children and adolescents is high [17,18] and air pollution may increase the associated costs [33], the results of the present study have substantial public health implications.

Previous studies exploring the association between ozone exposure and pneumonia among children and adolescents are relatively rare and have yielded heterogeneous results [12]. For example, a time-series study conducted in 17 states of the United States reported a positive association between ozone levels and emergency department visits due to pneumonia at 0–18 years of age [9], while another time-series study in Hanoi, Vietnam did not find an association between ozone levels and hospital admissions due to pneumonia at 0–17 years of age [11]. Furthermore, few studies have identified high-risk age groups by stratifying children and adolescents by age: Some studies suggested that associations between ozone and pneumonia ~~would~~ might be more prominent at 0–4 years of age than at older ages [13,14]. However, another

time-series study failed to identify an association between ozone and pneumonia at 0–1 and 1–5 years of age [11]. For older children and adolescents, a case-crossover study in California found no association between ozone levels and emergency department visits due to pneumonia at 5–18 years of age [13]. ~~Such~~ This observed heterogeneity may be attributable to differences in population characteristics (related, for example, to sensitivity and adaptive capacity), exposure levels, measurement error for exposure and outcome, and analytical strategies (e.g., study design, statistical models, and methods used to control for the confounding effects of various factors, including other air pollutants).

In the generalized difference-in-differences analyses, considering the effects of other air pollutants, we found an association between ozone levels and pneumonia at 0–4 and 5–9 years of age, but not at 10–14 or 15–19 years of age. It has been suggested that ozone exposure can increase the risk of airway infections by affecting host immunity [34,35]. Thus, the immature immune system of younger children may ~~be responsible for~~ explain these findings [36]. The results might also reflect lower rates of outdoor activity (and time spent outdoors) among middle- and high-school students compared with those of younger children in the Republic of Korea [37], given that indoor ozone levels are generally lower than outdoor levels [15].

Most previous studies [8,10,11,13,15], but not all of them [14], have reported a stronger association between ozone and pneumonia in warm than in cool seasons. These findings are inconsistent with the results of this study, which showed a stronger association in cool seasons. The reason for this inconsistency is not clear. However, although ambient ozone levels are lower in cool seasons, outdoor activities are likely to increase on sunny days with higher temperatures

333 (possibly days with higher ozone levels as well) in cool seasons but decrease on similar days in
334 warm seasons, resulting in different individual exposure patterns according to seasons [14]. In
335 addition, air conditioning with low ventilation due to closed windows in warm seasons
336 (especially on sunny days with higher temperatures) can also prevent the penetration of outdoor
337 ozone, hence reducing exposure [15]. Finally, the observed stronger association between ozone
338 and pneumonia in cool seasons might be affected by seasonal differences in ozone levels and
339 their variance (Supplementary Material 423) or the unmeasured confounding effect of seasonal
340 variations in infections. However, we found robust results in analyses further adjusted for
341 influenza epidemics.

342 This study has limitations. First, we used monitoring data for ozone levels from fixed sites as a
343 proxy for population exposure. Although this exposure assignment method is widely used in air
344 pollution epidemiology studies (especially those exploring the effects of short-term exposure to
345 air pollution) and ozone levels are spatially homogeneous compared with the levels of other air
346 pollutants [38], it reportedly produces the Berkson-type measurement error, leading to lower
347 precision rather than to bias [39]. Second, ~~there exists a concern of~~ outcome misclassification is a
348 concern. However, because we defined the outcome based on the principal diagnosis of hospital
349 admission due to pneumonia determined by a physician, problems related to the precision of the
350 diagnosis can be assumed to be low. In contrast, as we only analyzed relatively severe cases
351 leading to hospital admission, ~~the possibility~~ it remains possible that the association between
352 ozone and pneumonia would be attenuated after including relatively mild cases ~~remains~~. Third,
353 although negative control outcomes can be used to detect bias and strengthen causal inference ~~in~~
354 ~~the~~ using an observational study design [40], we could not apply them (e.g., hospital admissions

due to appendicitis) in the present study, due to the lack of sufficient information. Fourth, this study used all hospitalization cases, rather than hospitalizations only through the emergency room, as an outcome; therefore, a considerable proportion of hospitalizations might have been scheduled ones and not associated with ozone exposure, leading to bias the results toward the null hypothesis.

However, the present study has strengths that merit highlighting. First, this is one of a few studies that systematically evaluated the susceptible periods to ozone exposure regarding pneumonia among children and adolescents, who are considered vulnerable populations. Therefore, this study ~~can~~ provides valuable evidence to select priority target populations for public health interventions and policies. Second, because the present study included all cases of hospital admissions due to pneumonia among children and adolescents in the Republic of Korea during the study period (2011–2015), the possibility of selection bias is low. Third, to the best of our knowledge, this is the first study applying to apply a formal causal inference method to investigate the effect of ozone levels on pneumonia. Using a generalized difference-in-differences method, we could control for a wide range of confounders related to the spatial and temporal units of the study, thus substantially improving causal inference. Fourth, we assessed the independent effect of ozone on pneumonia by considering other air pollutants that can act as confounders. These analyses not only provide stronger evidence for a causal relationship, but also have direct public health implications, by aiding the formulation of air pollution standards for a specific air pollutant.

In conclusion, ~~compared with ozone levels of 40.0 ppb, ozone levels of 60.0 and 70.0 ppb were~~

associated with a higher risk of pneumonia at 0–4 and 5–9 years of age, but not at 10–14 or 15–19 years of age. ~~The associations between ozone and pneumonia at 0–4 and 5–9 years of age were also found at low ozone levels of 30.0 ppb (much below the current ozone standard of 60.0 or 70.0 ppb).~~ This study provides valuable insights to help identify vulnerable periods to ozone exposure in terms of pneumonia, determine the target populations for public health interventions and policies, and establish air pollution standards (considering the observed association between ozone and pneumonia below the current ozone standards). However, because the results of the present study might also reflect different differences in outdoor activity patterns by age groups as well as vulnerability, future studies involving a more precise estimation of ozone exposures ~~by~~ considering behavioral factors are needed.

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397 **Conflict of interests:** The authors declare that they have no competing interests.

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507

508 **Figure legend**

509 **Figure 1.** Concentration-response curves for the associations between ozone and pneumonia by
510 age group, estimated from the distributed lag non-linear models adjusted for region, day,
511 temperature, relative humidity, population, and other air pollutants (PM₁₀, NO₂, SO₂, and CO).

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Table 1. Daily hospital admissions due to pneumonia, air pollution, and meteorological factors in Korea, 2011–2015

	Mean (SD)	Percentile					IQR
		Min	25th	50th	75th	Max	
Daily counts of hospital admissions due to pneumonia							
0–4 years	493 (276)	88	295	424	633	2,507	338
5–9 years	100 (90)	6	46	70	114	726	68
10–14 years	29 (26)	0	12	21	35	274	23
15–19 years	12 (10)	0	6	10	15	117	9
Air pollution levels							
Ozone ^a (ppb)	37.3 (13.4)	6.8	26.8	36.5	46.7	90.3	19.9
PM ₁₀ ^b (µg/m ³)	46.4 (17.4)	11.6	34.4	43.6	54.9	203.0	20.6
NO ₂ ^b (ppb)	20.7 (8.9)	2.5	14.2	19.2	25.7	63.3	11.6
SO ₂ ^b (ppb)	4.8 (2.0)	1.0	3.3	4.6	6.0	17.3	2.6
CO ^b (ppb)	496.0 (150.3)	172.3	394.9	469.9	568.8	1,502.0	173.9
Meteorological factors ^c							
Temperature (°C)	13.2 (9.8)	-14.6	4.8	14.4	21.7	33.1	16.9
Relative humidity (%)	67.0 (15.2)	11.3	56.8	68.5	78.3	99.9	21.5

Abbreviations: SD, standard deviation; IQR, interquartile range

^aDistribution of 7-day moving averages of daily 8-hour maximum concentrations during the study period (2011–2015).

6 ^bDistribution of 7-day moving averages of daily mean concentrations during the study period
7 (2011–2015).

8 ^cDistribution of daily averages during the study period (2011–2015).

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10 **Table 2.** Cumulative effects of ozone levels up to 7 days on pneumonia^a, stratified by age group

	Not adjusted for other air pollutants ^b		Adjusted for other air pollutants ^b	
	60.0-70.0 ppb		60.0 ppb	70.0 ppb
	RR (95% CI)	95% CIRR (95% CI)	RR (95% CI)	95% CIRR (95% CI)
0-4 years	1.021.05 (1.02, 1.07)	(1.01, 1.03)1.06 (1.02, 1.09)	1.021.05 (1.02, 1.07)	(1.01, 1.03)1.06 (1.02, 1.09)
5-9 years	1.061.13 (1.08, 1.18)	(1.04, 1.08)1.16 (1.09, 1.24)	1.061.13 (1.08, 1.18)	(1.04, 1.08)1.16 (1.09, 1.24)
10-14 years	1.021.13 (1.05, 1.22)	(0.99, 1.05)1.13 (1.02, 1.25)	1.011.07 (0.98, 1.15)	(0.98, 1.04)1.03 (0.92, 1.15)
15-19 years	1.011.02 (0.92, 1.14)	(0.97, 1.06)1.06 (0.91, 1.23)	1.010.98 (0.87, 1.10)	(0.97, 1.06)0.98 (0.84, 1.15)

11 **Abbreviations:** RR, relative risk; CI, confidence interval

12 ^aCumulative effects were estimated for a 10.0-ppb increase in ozone levels of 60.0 ppb and 70.0
 13 ppb, with ozone levels of 40.0 ppb as a reference, after adjustment for region, day, temperature,
 14 relative humidity, and population (and PM₁₀, NO₂, SO₂, and CO in models further adjusted for
 15 other air pollutants).

16 ^bPM₁₀, NO₂, SO₂, and CO.

서식 있는 표

18 **Table 3.** Cumulative effects of ozone levels up to 7 days on pneumonia^a, by age and season

	Warm season (from May to October)		Cool season (from November to April)		서식 있는 표
	RR	95% CI	RR	95% CI	
0–4 years	1.01	(0.99, 1.02)	1.06	(1.04, 1.09)	
5–9 years	1.05	(1.02, 1.07)	1.07	(1.03, 1.12)	
10–14 years	1.03	(0.99, 1.07)	0.95	(0.88, 1.02)	
15–19 years	1.01	(0.96, 1.07)	1.09	(0.98, 1.20)	

	Warm season (from May to October)		Cool season (from November to April)		서식 있는 표
	60.0 ppb	70.0 ppb	60.0 ppb	70.0 ppb	
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	
0–4 years	1.03 (1.00, 1.07)	1.05 (1.00, 1.10)	1.16 (1.10, 1.21)	1.18 (1.10, 1.28)	
5–9 years	0.98 (0.92, 1.05)	0.94 (0.86, 1.03)	1.24 (1.12, 1.37)	1.07 (0.90, 1.27)	
10–14 years	1.00 (0.90, 1.12)	0.97 (0.84, 1.13)	1.04 (0.88, 1.22)	0.86 (0.65, 1.13)	
15–19 years	0.90 (0.78, 1.06)	0.91 (0.73, 1.13)	1.33 (1.06, 1.67)	1.26 (0.85, 1.87)	

20 **Abbreviations:** RR, relative risk; CI, confidence interval

21 ^aCumulative effects were estimated for a 10.0-ppb increase in ozone levelsozone levels of 60.0–
 22 ppb and 70.0 ppb, with ozone levels of 40.0 ppb as a reference, after adjustment for region, day,
 23 temperature, relative humidity, population, and other air pollutants (PM₁₀, NO₂, SO₂, and CO).

: $\llbracket i fY'\%$

0-4 years

5-9 years

10-14 years

15-19 years