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Long-Term Ozone Exposure, COPD, and Asthma Mortality: A Retrospective Cohort Study in the Republic of Korea

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Abstract: Ozone concentrations have increased in recent decades, and several studies have reported that long-term exposure to ozone increases the mortality risk induced by respiratory conditions. However, research on cause-specific mortality related to ozone exposure and respiratory diseases remains scarce. We constructed a retrospective cohort of 5,360,032 adults aged ≥ 65 years from the National Health Insurance Service of Republic of Korea, and death certificates were obtained from Statistics Republic of Korea to determine the cause of death between 2010 and 2019. The daily maximum 8 h average levels of ozone during the warm season annually (May–September) and other air pollutants were determined for the residential district. We analyzed the data using a time-varying Cox proportional hazards model with individual- and district-level covariates, incorporating a competing risk framework to address deaths from causes other than chronic obstructive pulmonary disease (COPD) and asthma. In our single-pollutant model with a 3-year moving average, a 1 ppb increase in ozone exposure was associated with a hazard ratio (HR) of 1.011 (95% confidence interval [CI]: 1.008–1.013) for COPD mortality and an HR of 1.016 (95% CI: 1.011–1.022) for asthma mortality. In our model adjusted for the presence of underlying diseases and district-level variables, the HRs were 1.009 (95% CI: 1.008–1.014) for COPD and 1.017 (95% CI: 1.011–1.023) for asthma, respectively. These associations remained robust in our two-pollutant model, except for NO_2 and COPD. A linear concentration–response relationship was identified between ozone concentration, COPD, and asthma mortality. In this large nationwide cohort study, long-term exposure to ozone was associated with an increased risk of death from COPD and asthma in older Korean adults.

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1. Introduction

As the global population ages, chronic respiratory diseases are becoming a prominent cause of death. The annual number of premature deaths due to chronic respiratory diseases is estimated as four million globally [1]. Chronic obstructive pulmonary disease (COPD) and asthma are chronic respiratory diseases that pose a significant global burden. COPD is a progressive airway disease [2], and asthma is a chronic inflammatory airway disease with a reversible airflow limitation and airway hyperresponsiveness [3]. According to the Global Burden of Disease Study 2019, mortality rates remain high, with 42.5 deaths per 100,000 population (37.6–46.3) for COPD and 5.8 deaths per 100,000 population (4.6–7.0) for asthma in 2019. The age-standardized Years of Life Lost due to COPD and asthma are 680.8 per 100,000 population (606.4–741.6) and 140.6 per 100,000 population (115.3–165.3) [4], respectively.

Ozone is an air pollutant that is predominantly generated during the summer season. As a potent oxidant, it can irritate the respiratory system and cause adverse health effects. Globally, while fine particulate matter ($PM_{2.5}$; another major air pollutant) has decreased in concentration over the past few decades, ozone concentrations have increased [5,6], especially in urban areas [7]. Recently, there has been a growing interest in studying the health effects of ozone to better understand its impact on human health. Studies have shown that long-term ozone exposure is associated with respiratory mortality [8,9]. Although several studies have reported the effects of long-term ozone exposure on COPD, the cause-specific mortality in other diseases have not been well-studied. For asthma, most previous studies on the association between ozone and asthma have focused on short-term ozone exposure [10,11]. Although the effects of long-term ozone exposure on asthma incidence is known [12,13], its effects on asthma-related mortality is limited.

In this study, we used a large cohort of the elderly population in Republic of Korea and employed a time-varying competing risk regression model to investigate the impact of long-term ozone exposure on mortality due to COPD and asthma.

2. Materials and Methods

2.1. Data Source and Study Participants

A retrospective cohort study was conducted based on the data provided by the National Health Insurance Sharing Service (NHISS) from the National Health Insurance Service (NHIS) of Republic of Korea. The NHIS is a single-payer program that is mandatory for all Korean residents and covers almost the entire Korean population. It comprises three main healthcare programs: National Health Insurance, Medical Aid, and Long-Term Care Insurance [14]. The NHISS data used in this study included age, sex, income, and home address at the district level. The cause of death statistics from Statistics Republic of Korea were linked to the cohort to obtain vital statuses and causes of death. The cohort was followed up from 1 January 2010, to 31 December 2019. The study population included adults aged $\geq$ 65 years as of 2010, totaling 5,562,993 individuals from the health insurance eligibility database. After excluding 201,804 individuals with missing information regarding age, sex, and income, with 1157 individuals who were registered as deceased before 2010, a final study population of 5,360,032 was enrolled.

This study was exempt from review by the Institutional Review Board of Seoul National University Hospital, Republic of Korea (IRB No. E-2105-043-1218) because not all personal information was accessed by the authors under the control of the NHIS.

2.2. Case Definition

We assessed data on death from COPD or asthma using death certificate data provided by Statistics Republic of Korea. Death caused by COPD was recorded if the primary or

secondary cause of death included codes J40–J44 from the International Classification of Diseases, 10th revision. Similarly, death caused by asthma was defined using the codes J45 and J46.

2.3. Air Pollution Data

We used the daily maximum 8 h average (MDA8) ozone concentration during the warm season (May–September) between 2010 and 2019. Hourly ozone exposure levels and air pollutants were modeled using Weather Research and Forecast, Sparse Matrix Operator Kernel Emission, and Community Multiscale Air Quality. Air pollutants included particulate matter in an aerodynamic diameter $\leq$10 μm (PM_{10}) and $\leq$2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) level. Air pollutant exposure levels were assigned by the district. Further details regarding exposure modeling and validation are available elsewhere [15,16]. For our time-varying Cox regression analysis, the exposure levels to air pollutants, including daily and warm season MDA8 concentrations, were assigned annually. The annual average ambient temperature and humidity data were collected from the Korean Meteorological Administration (https://www.kma.go.kr/, accessed on 6 November 2024).

To investigate the effects of different exposure periods, we constructed moving average models with time-exposure windows ranging between 1 and 3 years for each model, and analyzed the goodness-of-fit statistic for each model. The results (Supplementary Table S1) showed that the 3-year model had the lowest Bayesian Information Criterion value.

We extracted the residential address data to create an annual address variable. Exposure values were applied to the updated address if an address change occurred during the study period. In cases where administrative districts changed during the follow-up period, we reclassified the data based on the most recent administrative district (as of 2019). In these cases, we applied the pollutant concentrations according to the new address from the time of change.

2.4. Covariates

The study population was classified into two age groups: (1) 65–74 years and (2) >75 years old. The NHI data provided household income as a number ranging from 1 (lowest) to 20 (highest). If participants' health insurance eligibility indicated that they had received medical aid, they were classified accordingly. Using household income and health insurance eligibility data from 2010, we categorized income into six groups: Medicare, low/mid (1–12), or high (13–20). Residential areas were classified as metropolitan (Seoul, Busan, Daegu, Gwangju, Incheon, Daejeon, and Ulsan) or others.

The Charlson Comorbidity Index (CCI) developed in 1987 by Charlson et al. predicts mortality by weighing specific comorbid conditions. This tool is widely used by health researchers to measure the burden of various diseases [17]. We calculated the CCI scores using primary and secondary diagnostic codes from the NHIS healthcare visit history data from 2009 (i.e., 1 year before the baseline year of the study period). These included prior myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, liver disease, and diabetes. If there was no underlying disease corresponding to the CCI, the variable was classified as "no"; otherwise, it was classified as "yes".

2.5. Statistical Analysis

Participants were followed up until death, loss to follow-up, or the end of the study period. To investigate the association between long-term ozone exposure and death due to asthma or COPD, we adopted a time-varying Cox proportional hazards model [18]. In this model, age was used as a time scale to account for the effects of age on the outcome, and calendar year was used as a covariate. Competing risks of death from causes other than those of interest were considered using the Fine and Gray sub-distribution method [19,20].

Model 1, the basic model, included calendar year, sex, income level, and health insurance eligibility as covariates. Model 2 included CCI scores. Model 3 included variables at the district level, such as total population size, proportion of the population aged ≥ 65 years, proportion of the population with educational levels of high school or less, number of hospital beds per 1000 population, annual average temperature (°C), annual average humidity (%), and the standardized smoking rate. Annual time-varying covariates were considered: first, single-pollutant models, and, then, two-pollutant models were used to examine the independent effects of each pollutant after controlling for the other. To test the multicollinearity, the variation inflation factor (VIF) statistics were calculated.

Stratification analysis was performed for underlying diseases (yes; CCI ≥ 1 and no), sex, regions, income (high, mid/low, and Medicare), CCI (≥3 and <3), and age (≥75 and 65–74 years). The results from different exposure windows (1, 2, and 3 years of exposure to ozone) were compared, and the best-fitting model was observed after 3 years of ozone exposure. We used this time-exposure window for stratification analysis. The significance of difference in beta estimates and coefficients between the stratified variables was estimated by calculating the Z-score of the following equation, following the determination of the *p* value using the Z-score.

$$Z = \frac{\hat{\beta_{k1}} - \hat{\beta_{k2}}}{\sqrt{se(\hat{\beta_{k1}})^2 + \sqrt{se(\hat{\beta_{k2}})^2}}} \quad (1)$$

The exposure–response curves for 3-year exposure to ozone-, COPD-, and asthma-related deaths were plotted using natural cubic splines. Additionally, the association between all-cause mortality and long-term ozone exposure were analyzed. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R statistical software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). *p*-values (two-sided) of <0.05 were considered statistically significant.

3. Results

The total number of adults aged ≥ 65 years registered in the 2010 NHIS database was 5,562,993. We excluded participants with missing information regarding sex, age, income, or residential address (N = 201,184) and those who died before 2010 (N = 1157). The final number of participants was 5,360,032 (Figure 1).

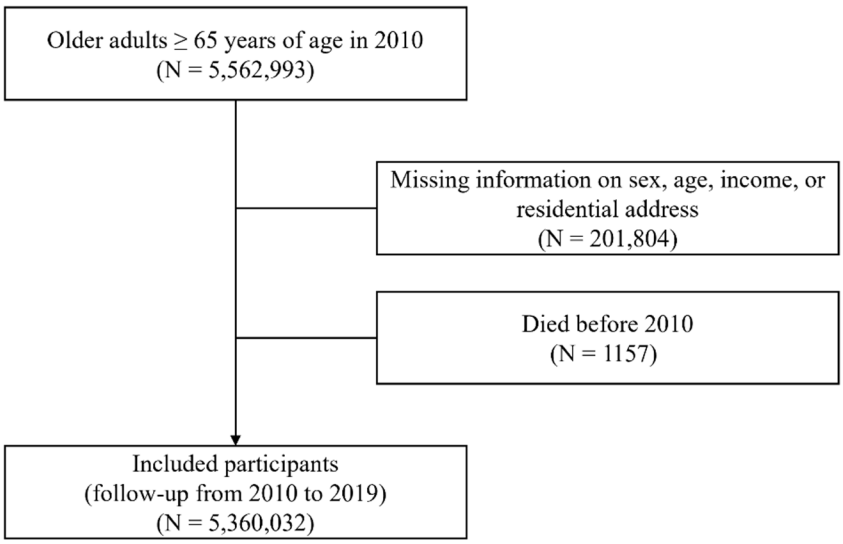

Figure 1. Depiction of the study population.

Table 1 presents the characteristics of the study participants. During the follow-up period, 46,228 and 12,308 participants died of COPD and asthma, respectively. Among

those who died of COPD, 31,957 (69.13%) were aged ≥ 75 years. Among those who died of asthma, 9577 (77.81%) were aged ≥ 75 years. More than half of those who died from COPD and asthma had an income below the low-income cut-off point. Regarding regional distribution, approximately 33% of participants lived in metropolitan areas and the remaining participants lived in other areas. The CCI score was 0 or 1 in slightly more than half of the patients who died of COPD or asthma.

Table 1. Characteristics of the study participants and deaths attributable to COPD or asthma.

Characteristics	Total		COPD Death		Asthma Death	
	N	%	N	%	N	%
Total	5,360,032	100.0%	46,228	0.9%	12,308	0.2%
Sex						
Men	2,193,175	40.9%	31,381	67.9%	4794	39.0%
Women	3,166,857	59.1%	14,847	32.1%	7514	61.0%
Age group						
65–74	3,372,719	62.9%	14,271	30.9%	2731	22.2%
75+	1,987,313	37.1%	31,957	69.1%	9577	77.8%
Underlying disease						
No	2,119,534	39.5%	12,284	26.6%	2593	21.1%
Yes	3,240,498	60.5%	33,944	73.4%	9715	78.9%
Income						
Medicare	466,464	8.7%	5722	12.4%	1700	13.8%
Low/Mid (1–12)	1,953,417	36.4%	27,178	58.8%	6743	54.8%
High (13–20)	2,940,151	54.9%	13,328	28.8%	3865	31.4%
Regions						
Metropolitan cities	2,189,845	40.9%	15,031	32.5%	4043	32.8%
Other areas	3,170,187	59.1%	31,197	67.5%	8265	67.2%
Charlson comorbidity score						
0	2,119,534	39.5%	12,284	26.6%	2593	21.1%
1	1,656,238	30.9%	16,831	36.4%	4643	37.7%
2	842,614	15.7%	9454	20.5%	2791	22.7%
3+	741,646	13.8%	7659	16.6%	2281	18.5%

Table 2 presents the annual MDA8 ozone concentrations during warm seasons. Between 2006 and 2019, the average ozone concentrations gradually increased in all areas. Regionally, the average ozone concentration was higher in all non-metropolitan areas. Distribution of mean maximum MDA8 ozone in the warm season by study participants are depicted in Supplementary Table S2.

Table 3 presents the hazard ratios (HRs) and 95% confidence intervals (CIs) for COPD and asthma mortality associated with long-term ozone exposure. In Model 1, using a 3-year moving average in our single-pollutant analysis, the HRs were 1.011 (95% CI, 1.008–1.013) for COPD mortality and 1.016 (95% CI, 1.011–1.022) for asthma mortality. In Model 3, which was adjusted for the CCI score and district-level covariates, the HRs were 1.009 (95% CI, 1.006–1.012) for COPD mortality and 1.017 (95% CI, 1.011–1.023) for asthma. In the two-pollutant model that included NO_2, the HR for COPD was 1.002 (95% CI, 0.998–1.005), indicating no statistical significance. For asthma, the HR was 1.017 (95% CI, 1.011–1.023), which was statistically significant. With the exception of the two-pollutant model with NO_2, the HR estimates in the two-pollutant models that included other pollutants were similar to those in the single-pollutant model. The VIF values ranged from 1.09 to 2.89, which means low multicollinearity between variables included in the models (Supplementary Table S3). The exposure–response curve between the 3-year moving average ozone exposure, COPD death, and asthma death showed a linear relationship (Figure 2). We could not find any evidence that there is a threshold at this level.

Table 2. Warm season (May–September) mean daily maximum 8 h average ozone levels during the study period.

	Year													
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Metropolitan cities														
Seoul	34.18	35.49	35.74	41.83	35.32	34.53	39.77	40.47	42.87	43.37	45.63	43.97	43.03	47.02
Busan	35.41	35.71	36.78	38.10	36.97	36.50	42.45	41.34	45.15	46.01	46.48	45.94	42.61	47.50
Daegu	38.76	40.12	47.43	43.50	43.94	44.71	46.82	49.52	50.01	53.17	50.22	52.64	45.86	51.30
Incheon	39.57	42.29	46.30	50.18	42.74	43.09	47.10	47.66	52.77	51.32	50.36	48.24	45.43	52.79
Gwangju	39.09	37.32	36.54	45.00	39.51	39.68	43.39	45.55	47.00	48.47	49.89	50.46	45.12	48.09
Daejeon	29.96	26.86	40.72	41.77	39.30	35.10	42.75	42.15	46.36	46.94	50.83	50.67	48.78	48.01
Ulsan	33.74	33.36	37.77	38.33	38.51	36.36	42.43	46.12	46.69	48.53	45.85	50.47	42.88	48.16
Other areas														
Gyeoonggi-do	39.69	41.52	41.51	47.12	41.43	41.51	46.88	46.86	50.08	51.52	52.52	49.75	48.56	54.99
Gangwon-do	44.45	44.46	45.83	49.66	44.95	45.20	45.73	47.69	54.60	52.90	52.17	51.02	48.64	51.58
Chungcheongbuk-do	41.91	40.91	42.65	49.12	44.40	44.21	46.09	50.20	52.19	51.83	52.89	53.54	48.85	52.61
Chungcheongnam-do	41.62	35.15	46.71	48.78	43.26	40.06	46.59	47.90	51.39	52.40	56.50	54.42	50.58	55.69
Jeollabuk-do	39.42	37.70	37.93	44.64	37.57	38.28	45.30	46.39	49.11	51.21	53.94	54.14	47.54	52.67
Jeollanam-do	43.39	45.18	45.04	49.03	43.44	44.53	46.97	50.28	50.28	53.13	53.38	54.24	46.98	51.31
Gyeongsangbuk-do	42.98	43.58	45.40	48.20	45.73	44.41	47.16	50.13	52.45	54.50	51.55	53.91	48.96	52.69
Gyeongsangnam-do	44.18	42.86	44.53	45.37	41.52	39.18	46.61	49.40	48.88	50.51	48.16	52.80	48.58	53.53
Total	40.16	40.17	42.32	46.12	41.48	40.88	45.44	46.96	49.57	50.67	50.95	50.97	47.21	51.94

Table 3. Results of time-varying Cox regression analysis for the association between deaths attributable to COPD or asthma and 1 ppb increase in ozone.

	COPD			**Asthma**		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
Exposure	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
1-year moving average						
Single-pollutant model	1.006 (1.003, 1.008)	1.006 (1.004, 1.008)	1.005 (1.002, 1.007)	1.009 (1.005, 1.013)	1.009 (1.005, 1.014)	1.009 (1.004, 1.013)
Two-pollutant model						
+$PM_{2.5}$	1.005 (1.003, 1.008)	1.006 (1.003, 1.008)	1.004 (1.002, 1.006)	1.009 (1.004, 1.013)	1.009 (1.005, 1.013)	1.008 (1.003, 1.012)
+PM_{10}	1.006 (1.003, 1.008)	1.006 (1.003, 1.008)	1.004 (1.002, 1.007)	1.009 (1.005, 1.013)	1.009 (1.005, 1.013)	1.008 (1.003, 1.012)
+NO_2	1.001 (0.999, 1.003)	1.001 (0.999, 1.003)	1.002 (0.999, 1.004)	1.007 (1.003, 1.012)	1.007 (1.002, 1.012)	1.008 (1.003, 1.013)
+SO_2	1.006 (1.003, 1.008)	1.006 (1.003, 1.008)	1.005 (1.003, 1.007)	1.010 (1.005, 1.014)	1.010 (1.006, 1.014)	1.009 (1.005, 1.014)
2-year moving average						
Single-pollutant model	1.007 (1.004, 1.010)	1.007 (1.004, 1.010)	1.006 (1.003, 1.008)	1.011 (1.006, 1.016)	1.012 (1.007, 1.017)	1.011 (1.006, 1.017)
Two-pollutant model						
+$PM_{2.5}$	1.007 (1.004, 1.010)	1.007 (1.004, 1.010)	1.005 (1.002, 1.008)	1.011 (1.006, 1.017)	1.012 (1.007, 1.017)	1.010 (1.005, 1.016)
+PM_{10}	1.007 (1.004, 1.010)	1.007 (1.005, 1.010)	1.005 (1.003, 1.008)	1.012 (1.006, 1.017)	1.012 (1.007, 1.017)	1.011 (1.006, 1.016)
+NO_2	0.999 (0.996, 1.002)	0.999 (0.996, 1.002)	1.000 (0.997, 1.003)	1.008 (1.002, 1.013)	1.007 (1.002,1.013)	1.009 (1.003, 1.015)
+SO_2	1.006 (1.004, 1.009)	1.006 (1.004, 1.009)	1.005 (1.003, 1.008)	1.012 (1.007, 1.018)	1.013 (1.007, 1.018)	1.012 (1.006, 1.017)
3-year moving average						
Single-pollutant model	1.011 (1.008, 1.013)	1.011 (1.008, 1.014)	1.009 (1.006, 1.012)	1.016 (1.011, 1.022)	1.017 (1.011, 1.022)	1.017 (1.011, 1.023)
Two-pollutant model						
+$PM_{2.5}$	1.011 (1.008, 1.014)	1.011 (1.008, 1.014)	1.009 (1.006, 1.012)	1.017 (1.011, 1.023)	1.017 (1.012, 1.023)	1.017 (1.011, 1.023)
+PM_{10}	1.011 (1.008, 1.014)	1.011 (1.008, 1.014)	1.009 (1.006, 1.012)	1.017 (1.011, 1.023)	1.017 (1.012, 1.023)	1.017 (1.011, 1.023)
+NO_2	1.000 (0.997, 1.004)	1.003 (1.002, 1.005)	1.002 (0.998, 1.005)	1.011 (1.005, 1.018)	1.011 (1.004, 1.018)	1.014 (1.007, 1.021)
+SO_2	1.009 (1.006, 1.012)	1.010 (1.007, 1.013)	1.008 (1.005, 1.012)	1.017 (1.011, 1.023)	1.018 (1.012, 1.024)	1.017 (1.011, 1.023)

COPD, chronic obstructive pulmonary disease; HR, hazard ratio; $PM_{2.5}$, particulate matter less than 2.5 μm in diameter; PM_{10}, particulate matter less than 10 μm in diameter; NO_2, nitrogen dioxide; SO_2, sulfur dioxide. Model 1 was adjusted for the calendar year, sex, income level, and health insurance eligibility. Model 2 included Charlson Comorbidity Index scores. Model 3 additionally included variables at the district level such as total population size, proportion of the population aged $\geq$ 65 years, proportion of the population with educational levels of high school or less, number of hospital beds per 1000 population, annual average temperature, annual average humidity, and standardized smoking rate.

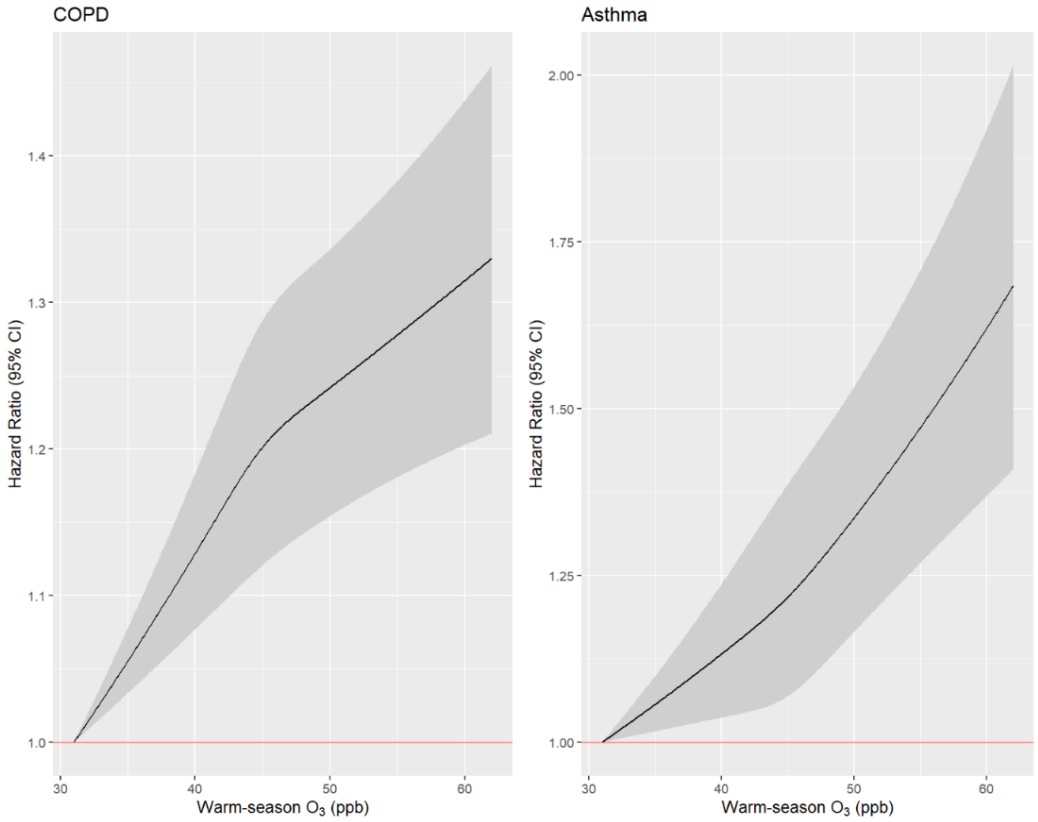

Figure 2. Exposure–response curve between long-term ozone exposure, COPD, and asthma mortality. COPD, chronic obstructive pulmonary disease; O_3, ozone. Hazard Ratios for COPD and asthma mortality according to the 3-year moving average ozone exposure were estimated with the adjustment of the calendar year, sex, income level, and health insurance eligibility, Charlson Comorbidity Index scores, and variables at the district level such as total population size, proportion of the population aged $\geq$ 65 years, proportion of the population with educational levels of high school or less, number of hospital beds per 1000 population, annual average temperature, annual average humidity, and standardized smoking rate.

Figure 3 and Supplementary Table S4 present the results of the stratified analysis. There were significant differences in COPD-related mortality according to the region and income level. In the high-income group, a one-unit increase in the 3-year average MDA8 ozone level was significantly associated with a higher risk of death from COPD (HR = 1.012, 95% CI = 1.008–1.106), with an HR value that was significantly different from that of the Medicare group (HR = 1.001, 95% CI = 0.993–1.008). The HR was significantly higher in metropolitan areas (HR = 1.022, 95% CI = 1.016–1.028) compared to other ones (HR = 1.004, 95% CI = 1.001–1.008).

The association between all-cause mortality and long-term ozone exposure was also significant (Supplementary Table S5). In Model 3, HRs for all-cause mortality by a 1 ppb increase in ozone in the 1-, 2-, and 3-year moving average were 1.002 (95% CI = 1.001–1.003), 1.004 (95% CI = 1.003–1.005), and 1.007 (95% CI = 1.006–1.008, respectively).

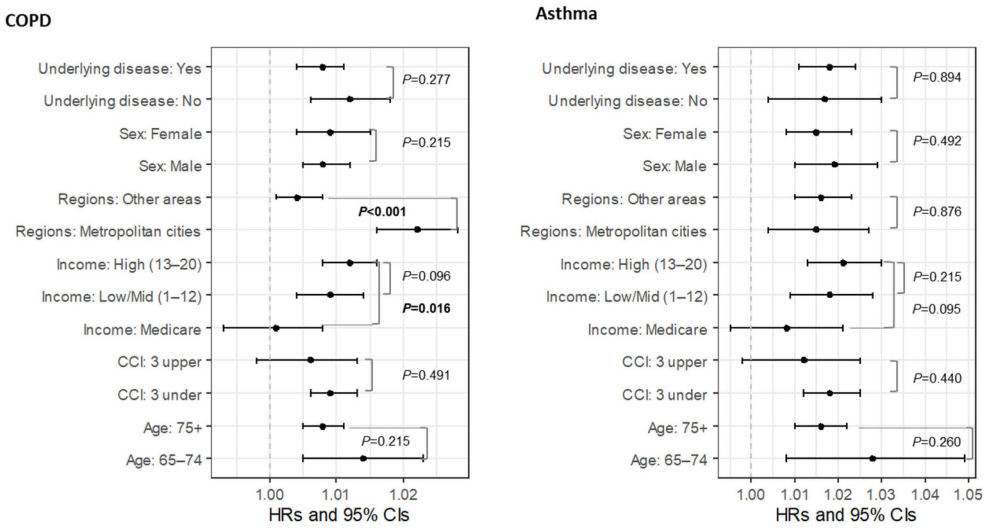

Figure 3. Stratified analyses of 3-year moving averages of ozone with mortality caused by COPD and asthma for the association between deaths attributable to COPD or asthma and 1 ppb increase in ozone. COPD, chronic obstructive pulmonary disease; HR, hazard ratio; adjusted for calendar year, sex, income level, and health insurance eligibility; Charlson Comorbidity Index scores; and variables at the district level such as total population size, proportion of the population aged ≥ 65 years, proportion of the population with educational levels of high school or less, number of hospital beds per 1000 population, annual average temperature, annual average humidity, and standardized smoking rate.

4. Discussion

In this large cohort study, long-term exposure to ozone was associated with an increased risk of mortality of COPD and asthma. The results were robust across models which accounted for various moving averages and covariates. This indicated that an increase in ozone levels cumulatively increased the relative probability of mortality of COPD or asthma.

These findings are consistent with those of previous studies that have reported a positive association between long-term ozone exposure and COPD-related mortality. The United States National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study [21] in a cohort study of 548,780 participants reported an HR of 1.05 (95% CI, 1.02–1.08) for COPD mortality per every 10 ppb increase in average ozone levels during the warm season (mean ozone level, 46.2 ppb). The study also showed that the significant association between ozone and COPD-related mortality remained robust in models adjusted for other pollutants such as $PM_{2.5}$ and NO_2, and the daily maximum temperature. In another US study, the Cancer Prevention Study-II (CPS-II) [22], in a cohort of 669,046 participants, reported an HR of 1.08 (95% CI, 1.05–1.12) for COPD-related mortality and similar conditions for every 1 ppb increase in average ozone levels during the warm season (mean level, 47.1 ppb). Similarly, in a study of 22.2 million Medicare beneficiaries in the US between 2000 and 2008 [23], the relative risk for COPD-related mortality for every 10 ppb increase in MDA8 ozone levels during the warm season was 1.084 (95% CI, 1.079–1.089). In another study that used Medicare data from 1985 to 2006 [24], every 5 ppb increase in average summertime ozone levels was associated with an HR increase of 1.07 (95% CI, 1.04–1.09) for COPD-related mortality.

Previous studies reported no significant association between long-term ozone exposure and COPD-related mortality. In a Canadian study [25], the MDA8 ozone concentration was 39.2 ppb and the age of the study population ranged from 25 to 89 years. In the ELAPSE pooled cohort study [26], the ozone concentration was 70 $\mu g/m^3$ (~35.7 ppb), and the mean age of the study population was 48.7 years. In these studies, the ozone concentrations were lower than that in our study. Furthermore, those studies included younger-age participants

and varying correlations between ozone and other air pollutants that may have resulted in a reduced impact of ozone on COPD-related mortality. In the current study, the estimated effect of ozone exposure on COPD-related mortality was relatively low compared to that reported in previous studies. This discrepancy may be attributed to the fact that previous studies included subjects of varying ages, whereas our study included only older adults. Consequently, the contribution of competing risks was higher in our study, leading to a relatively small estimate.

Studies on the association between long-term ozone exposure and asthma-related mortality are rare. Most studies focused on the effects of short-term ozone exposure on asthma-related mortality [11]. Additionally, studies that have investigated long-term ozone exposure have not typically analyzed asthma-related deaths as a separate outcome but, instead, have included a broader category of mortality caused by respiratory conditions [9,22,27]. In a case–crossover study conducted in China that included 4454 participants, an interquartile range increase in ozone levels (lag, 3 d; 52.9 $\mu g/m^3$) was associated with asthma-related mortality with an odds ratio of 1.09 (95% CI, 1.01–1.18) [11]. Several studies have explored the impact of long-term ozone exposure on asthma incidence. A cohort study conducted in Canada involving children showed that an incremental increase of 3.22 ppb in ambient ozone levels was associated with asthma onset with an HR of 1.11 (95% CI: 1.10–1.12) [28]. Another study in China demonstrated that long-term exposure to ozone levels > 38.17 ppb was associated with adult-onset asthma with an HR of 1.204 (95% CI, 1.168–1.242) [12].

In this study, a linear concentration–response relationship was observed between ozone concentration and COPD- and asthma-related mortality. In the CPS-II study [27], a threshold of ~56 ppb was identified in the concentration–response curve between long-term ozone exposure and death caused by respiratory conditions. However, a subsequent NIH-AARP study [21] did not identify this threshold. Consistent with this finding, this study found no evidence supporting the existence of such a threshold.

In our analysis stratified by sex, age, underlying disease, residential area, income level, and CCI, the association between COPD mortality and $PM_{2.5}$ showed significant differences according to region and income level. However, no significant differences in asthma-related mortality were observed in any of these variables. Generally, higher-income groups living in urban areas tend to have better living conditions and more green space around their homes [29]. However, the vulnerability to ozone by income status has not yet been confirmed [30]. The high-income group had a significantly higher HR than the Medicare group (p = 0.016) in our study. It does not imply the high-income group is more vulnerable compared to the low-income group. The life expectancy of medical aid beneficiaries in Republic of Korea has been reported to be lower, with an average life expectancy of 70.9 years in 2017—which is ~13 years shorter than the 83.7 years reported for National Health Insurance beneficiaries [31]. Therefore, the bigger association between ozone and COPD mortality among the high-income group may be because of the premature death from causes other than COPD among the low-income group. Considering that higher-income older adults tend to live longer than those with a lower income, the higher-income individuals were, on average, older. COPD prevalence increases with age, particularly in males, those with a history of smoking, and individuals with a lower income [32]. The prevalence of COPD tends to be higher in lower-income groups, a trend previously reported in Republic of Korea [33,34]. Regarding healthcare accessibility, low-income groups may experience delays in diagnosis and treatment, leading to early mortality other than COPD. A recent study showed that delays in the diagnosis and treatment of COPD and asthma resulted in poor outcomes [35]. Therefore, considering that the participants in this study were older, the observed lower impact of ozone exposure in the low-income group may be partially explained by survivorship bias. This suggests that the higher risk may not necessarily be because the high-income group is more affected by ozone, but, instead, because individuals with poorer health in the low-income group may have died earlier. Additionally, the relatively low impact of ozone may be caused by poor outcomes

resulting from delayed diagnosis and treatment. Although not statistically significant, a similar trend was observed in asthma, supporting this explanation. The mean ozone concentration was higher in non-metropolitan areas; however, the ozone-induced HR for COPD-related mortality was higher in metropolitan areas. Considering previous studies on health inequality in Republic of Korea, which indicated that mortality and unhealthy behaviors were higher in rural areas than in urban areas [36–38], these results could be interpreted in a context similar to the results of our income-stratified analysis, suggesting that the findings might be influenced by a survivorship bias caused by earlier deaths among residents of non-metropolitan areas.

Ozone is a potent oxidant that induces reactive oxygen species generation in the airways and promotes inflammatory responses and hyper-responsiveness [39]. Ozone exposure triggers the release of inflammatory cytokines in cells, induces mitochondrial dysfunction, and causes inflammatory responses and apoptosis through the activation of cellular signaling pathways, leading to a decrease in lung function and an increased risk of developing emphysema [40]. In animal studies, prolonged exposure to ozone induced chronic inflammation and structural changes in the small airways [41,42]. In human epidemiological studies, long-term exposure to ozone has been observed to impair lung development and decreases lung function in both children [43] and adults [44,45]. A recent study in China demonstrated that long-term exposure to ozone is associated with the acute exacerbation of COPD, leading to increased hospital readmission rates [46].

Exposure to ozone increases hyper-responsiveness in patients with asthma, making the airways more sensitive to allergens [47] and enhancing the eosinophilic airway response [48]—which further exacerbates asthma symptoms. Long-term exposure to low concentrations of ozone has been shown to increase airway hyper-responsiveness in sensitized animals [49]. The acute exacerbation of asthma caused by short-term exposure to ozone has been well-established [50], and prolonged exposure to ozone can lead to increased airway inflammation and hyperresponsiveness, potentially resulting in worsened asthma and increased mortality.

This study had several strengths. We assessed the causes of death in nearly all Koreans aged $\geq$ 65 years by linking large-scale data from the NHIS and mortality data from Statistics Republic of Korea over 10 years. Thus, we obtained objective information regarding the underlying diseases, addresses, and causes of death using nationally certified statistical data. This study population was large and encompassed almost the entire population of older adults living in Republic of Korea. Moreover, we confirmed the robustness of our findings by considering various models and covariates, including the medical history.

This study had several limitations. First, we could not ascertain the individual smoking history or the severity of any underlying diseases that may have affected mortality. A history of smoking is a major risk factor for the development and exacerbation of COPD [51] and asthma [52,53]. Although we used few district-level covariates, including standardized smoking rates and educational levels, residual confounding may still exist, as these were not individual-level data. Nevertheless, several similar studies used the county-level smoking prevalence instead of individual-level data [54,55]. Owing to the lack of a direct association between smoking status and air pollution, it may not be appropriate to consider smoking status as a confounder. Second, we used residential address data to evaluate ozone exposure, which may not accurately reflect the actual exposure if daily activities occur in different locations. We could not assess the indoor ozone exposure levels and account for the differences in ozone exposure caused by variations in individual outdoor activity times. Therefore, the misclassification of ozone exposure levels may have occurred. However, this limitation may have been partially offset by older adults generally having smaller living radii and shorter daily trip distances than younger individuals [56,57]. Third, deaths were defined as those caused by COPD or asthma when listed as either primary or secondary diagnoses on deceased individuals' death certificates. However, some individuals with multiple underlying conditions may have inaccuracies on their recorded death certificates. This misclassification could have reduced the observed effect size. Finally, this study was

conducted using data from older Koreans; therefore, the findings cannot be generalized to other races or age groups. Ozone levels are increasing worldwide, and the number of ozone warnings and alerts issued annually in Republic of Korea has been increasing. With the growing population of older adults in the country who are more vulnerable to ozone exposure, new policies for managing ozone levels are warranted.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/atmos15111340/s1, Supplementary Table S1: Goodness-of-fit of models and different moving average periods. Supplementary Table S2: Distribution of mean maximum 8 h average ozone in warm season by study participants. Supplementary Table S3: Variation Inflation Factor (VIF) values for the two pollutants in two-pollutant models. Supplementary Table S4: Results of stratified analyses of time-varying Cox regression for the association of deaths due to COPD and asthma mortality with ozone. Supplementary Table S5: Results of time-varying Cox regression analysis of association between all-cause mortality and 1 ppb increase in ozone.

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