REVIEW

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# Health Effects of Ozone on Respiratory Diseases

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Ozone is known to cause bronchial inflammation and airway hyper-responsiveness via oxidative injury and inflammation. While other ambient air pollutants such as particulate matter (PM) and nitrogen dioxide showed decreasing trends in mean annual concentrations, ozone concentrations have not declined recently in most countries across the world. Short-term exposure to high concentrations of ozone has been associated with increased mortality and cardiovascular and respiratory morbidity in many regions of the world. However, the long-term effects of ozone have been less investigated than the short-term exposure due to the difficulty in modeling ozone exposure and linking between individual exposures and health outcome data. A recently developed model of ozone exposure enabled the investigation of long-term ozone effects on health outcomes. Recent findings suggested that long-term exposure to ozone was associated with an increased risk of cardiovascular and respiratory mortality. Longitudinal studies using large cohorts also revealed that long-term exposure to ozone was associated with a greater decline in lung function and the progression of emphysema. The development of long-term standards for ozone as well as PM should be considered to protect the respiratory health of the general population and people with chronic respiratory diseases.

**Keywords:** Asthma; Chronic Obstructive Pulmonary Disease; Interstitial Pulmonary Fibrosis; Ozone

## Introduction

According to global burden of disease attributed to ozone exposure, 254,000 global excess mortality were reported in 2015[1]. This is ten times less than that attributable to particulate matter 2.5 ($PM_{2.5}$), which was 4.2 million death in 2015. Mortality due to ozone exposure may seem trivial compared to the number of deaths associated with $PM_{2.5}$, but it is more widely distributed worldwide[1]. As the aging population grows, air pollution has become a bigger problem in the Asia-Pacific region than before[2]. Due to constant efforts to mitigate air pollution in many countries, air quality has improved. Nonetheless, even though annual average concentrations of fine particulate matter and nitrogen dioxide have decreased since 2000, annual ozone levels continue to increase[3]. On an individual level, it is recommended that susceptible individuals avoid outings on days when ozone level is high. While smoking cessation is mainly a consequence of personal efforts[4], mitigation of ambient air pollution also depends on national policy and regulation. In Korea, 8-hour average ozone standard is currently set to be 60 parts per billion (ppb), but there is no standard on long-term standards such as mean annual concentrations. This paper emphasizes the continual need to analyze the existing standards to improve and protect population health.

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## Short-Term Exposure to Ozone and Respiratory Diseases

### 1. Overview

There is ample evidence that supports the association of short-term ozone exposure and respiratory health outcomes in terms of mortality and exacerbations. To evaluate short-term effects of ozone exposure, time-series or case-crossover study designs that aim to assess whether there is an increase in mortality or hospital admission or visits to emergency department (ED) soon after ozone level increases are widely used.

### 2. Mortality

Many studies have demonstrated that short-term ozone exposure increased total mortality, respiratory and cardiovascular mortality globally[5-7]. Short-term warm-season ozone exposure was associated with increased risk of mortality in the U.S. Medicare population data[8]. This study also highlighted that this risk occurred at levels below current national air quality standards. The association between short-term exposure and mortality was also reported in East Asia[9]. This study also showed that ambient ozone was associated with an increased risk of mortality in a relatively low range of levels in Korea, Japan, and Taiwan.

When meteorological factors were taken into consideration, lung cancer mortality risk increased during the warm season, especially in men and elderly patients[10]. Considering that lung cancer occurs predominantly in the elderly, close attention should be given and specific management should be considered[11]. During the warm/summer season, for example, elderly patients should try to stay inside during daytime in order to prevent ozone exposure as much as possible. Such recommendation may lead to a decrease in physical activity although evidence shows the benefits of physical activity even in polluted areas[12]. Therefore, potential risks and benefits should be well-evaluated in the future guidelines.

### 3. Respiratory outcomes

A recent systemic review and meta-analysis indicated that short-term ozone exposure was associated with an increased risk of chronic obstructive pulmonary disease (COPD) hospitalizations[13]. Furthermore, recent study reported that ozone level was associated with COPD incidence[14]. A higher number of hospitalizations and ED visits reflect poor prognosis of COPD patients and place an enormous economic burden not only on the patients, but also on national medical costs[15].

Interstitial pulmonary fibrosis (IPF) is another chronic respiratory disease that should be paid attention to as it is the most common and severe form idiopathic interstitial pneumonia[16]. While several papers reported that traffic-related air pollution is associated with poor outcomes including mortality and hospital admission in IPF patients[17-19], effects of ozone should yet to be investigated in depth.

Ozone exposure was known to increase asthma exacerbations[20]. According to recent report, short-term exposure of ambient ozone increased ED visits due to asthma in children throughout the Pittsburg area at lag day 1 (odds ratio, 1.12; 95% confidence interval [CI], 1.03–1.22; $p<0.05$)[21].

Of interest, when age-specific effects of $PM_{2.5}$ and ozone on ED visits due to respiratory diseases including acute respiratory infection, asthma, and COPD were evaluated, children were found to be more susceptible to $PM_{2.5}$ while the elders were more vulnerable to ozone[22]. This study suggested that elderly subjects may be more susceptible to ozone due to physiological and structural change.

### 4. Mechanism of injury

Ozone exposure triggers bronchial inflammation and hyper-responsiveness; respiratory tract oxidative stress leads to allergic sensitization, morphological changes of the tract, and impaired host defense[23]. The increased airway responsiveness then causes airway obstruction and decrements in lung function. Furthermore, sensory nerves in respiratory tract as well as local reflex responses are activated, diminishing inspiratory capacity and incurring pain on inspiration.

## Association with Long-Term Exposure to Ozone in Epidemiological Studies

### 1. Overview

Epidemiological evidence of the association of long-term exposure to ozone is remarkably limited compared to the association of short-term exposure. Although many toxicological studies and controlled exposure studies consistently suggested the association, there have been relatively fewer epidemiological studies that showed the association particularly for incidence[24,25]. This limited evidence is also different from other pollutants. While large cohort studies in North America, Europe, and Asia consistently reported the association of long-term exposure to particulate matter and nitrogen dioxide with mortality, lung cancer, and cardiovascular and respiratory diseases[26], findings for ozone remained inconsistent. Based on these inconsistent findings, the comprehensive review report of the U.S. Environmental Protection Agency (U.S. EPA) focusing on ozone concluded that the causal association of long-term exposure to ozone is only suggestive[24]. The association of long-term ozone was relatively stronger in a few respiratory outcomes including incidence of asthma than other major endpoints such as mortality, cardiovascular


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diseases, and lung cancer. A few recent studies have expanded the outcomes of interest and found the associations with subclinical cardiovascular and respiratory endpoints. These studies adopted advanced exposure prediction approaches to estimate individual-level exposure to ozone. One of the recent advances in epidemiological studies of assessing the impact of long-term air pollution is the development of exposure prediction approaches to overcome unavailability of individual exposure measurements[27]. Cohort studies of air pollution have developed simple to advanced exposure prediction models to estimate individual-level long-term concentrations at people's homes and work. As there have been relatively fewer cohort studies for ozone than for other pollutants, ozone prediction models were recently adopted and contributed to finding of new evidence of the association. Whereas long-term exposure to air pollution was generally assessed as average concentrations of 24-hour means over one to multiple years, most studies of ozone used warm-season averages of 1 or 8-hour maximum to represent large production of ozone derived by chemical reaction with sunlight and high temperature.

## 2. Mortality

Although some cohort studies in the United States and Canada reported the modest association of long-term exposure to ozone and non-accidental mortality[28-31], other cohort studies in the United States, Europe, and Asia reported no association[32-34]. A large cohort study in the United States including 60 million Medicare beneficiaries over 65 years old in the continental United States for 2000–2012 estimated individual-level warm-season exposure to ozone based on zipcode-level addresses using a previously validated exposure prediction model[31]. They found that a 10 ppb increase in ozone was associated with a 1% (hazard ratio [HR], 1.01; 95% CI, 1.01–1.01) increase in non-accidental mortality. Canadian studies of 2–3 million people in the Canadian Census Health and Environment Cohort (CanCHEC) followed for more than 10 years estimated warm-season postal-code residential concentrations using an exposure prediction model, and found 8% (HR, 1.08; 95% CI, 1.02–1.24) and 7% (HR, 1.07; 95% CI, 1.06–1.08) increases in non-accidental mortality[28,30]. Estimated risk for respiratory mortality tended to be stronger in the American Cancer Society (ACS) cohort in the United States[29,35], but other cohort studies in Canada, England, and France reported no association[32,33,36]. The first ACS study used 450 thousand people living in metropolitan areas of the United States with 18 years of follow-up period, and assigned city-wide averages of regulatory monitoring data for 1997–2000[35]. While ozone was not associated with total mortality, they found that a 10 ppb increase in ozone was associated with a 4% increase in respiratory mortality (HR, 1.04; 95% CI, 1.01–1.07). A follow-up study that expanded the population and focused on specific respiratory mortality found 10% (HR, 1.10; 95% CI, 1.03–1.18) and 14% (HR, 1.14; 95% CI, 1.08–1.21) increases in pneumonia and COPD mortality, respectively[29]. Studies of the association with cardiovascular mortality largely reported inconsistent findings.

## 3. Respiratory and cardiovascular outcomes

Evidence of long-term ozone and respiratory health was mostly obtained from asthma incidence in children. The Children's Health Study (CHS) that followed up approximately 4,000 children in 12 communities in California, USA since 1993 found that children living in the communities with decreased ozone concentration over almost 20 years from 1-year concentration at baseline showed decreased asthma incidence compared to those living in the communities with increased ozone[37]. In the early CHS data with 5-year follow-up, children in the communities with high ozone concentration showed higher incidence when exercised more compared to those exercised less[38]. A Canadian study based on the Quebec Integrated Chronic Disease Surveillance System cohort with 2-year follow-up also showed the association with asthma onset. Using 1 million children and their summertime ozone concentrations estimated at zip-code addresses at birth, a 10 ppb increase in ozone was associated with 38% increase in asthma onset (HR, 1.38; 95% CI, 1.34–1.42)[39]. Other studies investigated the associations with lung function, lung development, respiratory infection, and allergic sensitization, but findings were mostly inconsistent[40-42]. Recently, the Multi-Ethnic study of Atherosclerosis and Air Pollution (MEAS Air) developed a spatio-temporal prediction model to estimate individual-level long-term ozone concentrations of about 6,000 health adults over 45 years old and living in six major US cities. Using percent emphysema obtained by cardiac computed tomography scan, this study found the association with greater increase in percent emphysema at baseline (0.43 for 10 ppb increase in ozone; 95% CI, 0.10–0.80) as well as during follow-up (0.60; 95% CI, 0.27–0.93)[3]. Long-term ozone was associated with lung function, emphysema severity, respiratory symptoms, and exacerbations in a heavy smoker cohort with or without COPD[43]. Findings of cardiovascular outcomes have been sparse. A few recent cohort studies focused on subclinical atherosclerosis assessed by carotid intima media thickness (CIMT) from ultrasound imaging in college students in the Testing Responses on Youth (TROY) study and healthy adults of MESA Air. The TROY computed different exposures according to different periods based on regulatory monitoring data and residential addresses, and found the associations using elementary school exposure (10.1 μm; 95% CI, 1.8–18.5) but not for early childhood and lifetime exposures[44]. In the MESA Air, baseline exposure was associated with a greater increase in CIMT over 10 years (18.7 μm; 95% CI, 4.7–32.3)[45].

## Conclusions

There are evidences for adverse health effects of short-term ambient ozone exposure. We should consider such adverse events occurred under the current standards, and a suspected increase in ozone level due to climate change when making future environmental policy. There has been emerging research interest in the health effect of long-term exposure to ozone, as recent findings suggested the associations with respiratory and cardiovascular outcomes accompanied by advanced exposure assessment mostly in large U.S. cohort studies. However, findings were still limited and inconsistent. In particular, there has been only one study that investigated the association with long-term ambient ozone in other regions than North America and Europe. This South Korean study reported a negative association with non-accidental mortality[34]. Methodological limitations such as no adjustment for other pollutants and potential measurement error resulting from limited monitoring data were also indicated as challenges to assess the valid association. Future studies need to apply local exposure prediction models to assess accurate individual exposure and to investigate expanded health endpoints in well-designed cohort studies focusing on diverse population.

## Authors' Contributions

Conceptualization: Kim WJ. Writing - original draft preparation: Kim SY, Kim E. Writing - review and editing: Kim WJ. Approval of final manuscript: all authors.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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