Human Health Effects of Ozone: The State of Evidence Since EPA’s Last Integrated Science Assessment
Human Health Effects of Ozone: The State of Evidence Since EPA’s Last Integrated Science Assessment

Authors

Stephanie M. Holm MD MPH
University of California, Berkeley

John R. Balmes MD
University of California, Berkeley

Ananya Roy ScD
Environmental Defense Fund
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Executive summary

Decades of research on ground level ozone show significant health effects on populations across the globe. Recent studies estimate that ozone exposure causes approximately 5,000 premature deaths per year in the United States.\textsuperscript{1,2} The Clean Air Act (CAA) mandates the establishment and revision of National Ambient Air Quality Standards (NAAQS) for criteria air pollutants like ozone to ensure protection of public health. During the review of the NAAQS, the U.S. Environmental Protection Agency (EPA) produces an Integrated Science Assessment (ISA) that represents an evaluation and synthesis of the most policy-relevant science. The last ISA for Ozone and Related Photochemical Oxidants\textsuperscript{3} was carried out in 2013. It reviewed the short- and long-term health effects of ozone and only the relationship between ozone and short-term respiratory effects was determined to be a causal relationship.

In the last five years, substantial further study of ozone’s health effects has been completed, with much of that work occurring at exposures below the current NAAQS. This review of over 275 studies was performed to understand the state of evidence on health effects of ozone, both in children and adults since the 2013 ISA.

Key findings:
The reviewed evidence indicates that ozone significantly increases the risk of:

- Respiratory disease: reduced lung function, hospital admissions and emergency department visits for asthma and respiratory infections and possibly increasing rates of asthma development. School-aged children are particularly vulnerable and the majority of the studies show stronger adverse effects of ozone at this critical stage of life.
- Cardiovascular disease: specifically increased rates of strokes. There is also accumulating evidence supporting ozone’s effects on cardiac arrhythmia in persons with preexisting heart disease.
- Mortality due to short-term exposure to ozone. Evidence suggests that the effects of ozone are stronger in extreme weather (hot or cold); that women and elderly are more susceptible. New studies are adding to the evidence that long-term exposure to ozone also increases rates of mortality.
- During the last ISA there was only one epidemiological study of the effects of ozone on central nervous system. Since then there have been several studies published, and though the emerging literature is not definitive, it suggests that ozone exposure could be associated with nervous system dysfunction resulting in increased risk of autism in children and possibly dementia among the elderly.

Importantly most of these studies span exposure levels well below the current standard of 70 ppb averaged over 8 hours indicating that the current standard is not protective of the health of children and families exposed to ozone across the United States and needs to be strengthened.

There is accumulating evidence of the long-term impacts of ozone on mortality, autism and dementia. EPA should also consider a developing a standard that encompasses a longer averaging time in order to protect the
public from the adverse effects of chronic exposure and not just daily spikes in ozone levels.
Introduction

Decades of research on ground-level Ozone (O₃) show significant health effects on populations across the globe and it has been estimated to cause 5,000 premature deaths per year in the United States. The Clean Air Act (CAA) mandates the establishment and revision of National Ambient Air Quality Standards for criteria air pollutants like Ozone. It directs the EPA Administrator to set primary NAAQS which “accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health” and “the attainment and maintenance of which ... [allow] an adequate margin of safety”.

Whenever the agency is reviewing a NAAQS for one of the six criteria pollutants, the U.S. Environmental Protection Agency (EPA) produces an Integrated Science Assessment (ISA) that represents an evaluation and synthesis of the most policy-relevant science. The ISA for a criteria pollutant is intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health..."

The last ISA for Ozone and Related Photochemical Oxidants was carried out in 2013, and in it, only the relationship between ozone and short-term respiratory effects was supported by sufficient evidence to consider it causal. Some relationships with ozone were considered to be likely causal, including those with long-term respiratory effects, short-term cardiovascular effects and mortality effects. Based on that review the NAAQS for ozone was decreased from 75 to 70 ppb over an 8-hour averaging time by the EPA Administrator.

Table 1: EPA 2013 ISA Causal Determination

<table>
<thead>
<tr>
<th>Health effect category</th>
<th>Short term exposure</th>
<th>Long term exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory effects</td>
<td>Causal relationship</td>
<td>Likely to be a causal relationship</td>
</tr>
<tr>
<td>Cardiovascular effects</td>
<td>Likely to be a causal relationship</td>
<td>Suggestive of a causal relationship</td>
</tr>
<tr>
<td>Central nervous system effects</td>
<td>Suggestive of a causal relationship</td>
<td>Suggestive of a causal relationship</td>
</tr>
<tr>
<td>Reproductive &amp; developmental effects</td>
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<td>Suggestive of a causal relationship</td>
</tr>
<tr>
<td>Other health effects</td>
<td>Inadequate to infer a causal relationship</td>
<td>Inadequate to infer a causal relationship</td>
</tr>
<tr>
<td>Total mortality</td>
<td>Likely to be a causal relationship</td>
<td>Suggestive of a causal relationship</td>
</tr>
</tbody>
</table>

Adapted from U.S. EPA. Integrated Science Assessment for Ozone and Related Photochemical Oxidants Feb 2013

In the last 5 years, substantial further study of ozone’s health effects has been completed. This work provides a summary of the accumulated evidence of ozone human health effects research that has been completed from 2013 onward.
This review was performed to cover all recent work on health effects of ozone, both in children and adults since the 2013 ISA, with particular attention to whether there were effects below the current NAAQS. We searched PubMed, CrossRef and Google Scholar using the search terms “health AND ozone”. Articles were selected for review if they involved work in humans (rather than in animals or in vitro research) and reported effects for ozone specifically. The initial search generated 1762 search results, of which 280 ultimately met our criteria and are summarized here (see Figure 1). For the purposes of this summary, we standardized results to be per 10 ppb increment in ozone (unless otherwise specified); for results that had been reported in µg/m³ an approximate conversion factor of 2 was used. Study quality was also assessed regarding confounding, bias and generalizability.

The 2013 ISA³ was organized into groupings by health effect, which we have replicated here. The following categories are reviewed: respiratory effects, cardiovascular effects, central nervous system effects, reproductive and developmental effects, and mortality.

Figure 1. Search Strategy for Ozone Studies
Respiratory Effects

In their last assessment, EPA determined that short-term exposure to ozone caused respiratory disease and long-term exposure likely caused respiratory disease. In particular EPA concluded that exposure induced decreases in lung function and pulmonary inflammation at concentrations as low as 60 ppb\(^3\) and that there was evidence that elevated ozone days increased respiratory symptoms and pulmonary inflammation in children with asthma; respiratory-related hospital admissions and ED visits; and respiratory mortality. Long-term epidemiological studies supported the likely causal effects of ozone with adverse respiratory symptoms, new-onset asthma and respiratory mortality exposure to ozone.

The studies reviewed below build upon the comprehensive body of literature reviewed previously in the 2013 ISA.

Asthma
Emergency room visits and hospital admissions

Epidemiological evidence since the last ISA continues to support a strong relationship between short-term ozone exposures and increases in asthma emergency department (ED) visits. Studies have recently used comprehensive public health databases of emergency department visits, which include records of all ED visits in those areas, over recent 5 to 10 years in Atlanta, Dallas, St Louis, Indianapolis, New York City and Eerie county in New York, Maricopa county in Arizona, the states of Georgia, North Carolina and California. A majority of these studies find that elevated ozone days are followed by increased rates of asthma ED visits, where a 10-ppb increment in short-term ozone (ranging from same day up to a 3-day average ozone) was associated with increases of 1.1%-4.2\(^6\)-8 in ED visits for asthma. A study in Newark, New Jersey also suggested an increased risk of ED visits of 3-7% with increased ozone, regardless of whether the data were analyzed in an ecologic, case-crossover or case-control fashion,\(^9\) further corroborating the robustness of the association.

Eight other case-crossover studies have also shown increases in odds of ER visits or clinic visits with odds ratios (ORs) that range 1.03-1.17 per 10 ppb ozone,\(^10\)-16 or an increase of 3% risk per 10 ppb ozone.\(^17\) One study in Japan showed a much higher OR (2.3) for specifically nighttime primary care visits for asthma.\(^18\) However, studies in France and Japan found no significant effects of ozone on asthma emergency or primary care visits.\(^18,19\)

Most studies indicated that school aged children were more susceptible and had higher rates of ED visits associated with ozone exposure. Studies also showed that the effect of ozone on ED visits for asthma seemed to occur with a shorter lag time in older adults, those in poverty, disadvantaged and minority communities,\(^10,6,14\) and in children who were born premature.\(^14\)
Similarly, most studies show a consistent effect of short-term ozone concentration on asthma hospital admissions. There are six new ecologic studies of asthma hospital admissions and ozone with a 10-ppb increase in short-term ozone (up to a 5-day average) associated with an 4-11% increase in admissions in most studies, although one study showed an inverse effect.

Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when you breathe), chest tightness, shortness of breath, and coughing. In the United States, more than 26 million people are known to have asthma, of which 6 million are children. CDC estimates that asthma costs the U.S. economy more than $80 billion annually in medical expenses, missed work and school days and deaths.

One of these studies, Zu et al. in 2017, assessed the impact of ozone on hospital admissions, from 2001-2013, in cities in Texas (El Paso, Austin, Dallas, Houston, Fort Worth, San Antonio) and found that in the populations residing in these cities, children were most at risk of asthma related hospitalization associated with elevated ozone. Furthermore, the effects were seen well below the current standard of 70 ppb. A case-crossover study in New York found a 6-13% increase in asthma admissions among school aged children per 10-ppb increment of ozone. These studies represent the effect
of ozone on hospital admissions in different parts of the world, such as Hong Kong, Australia, the United States and Canada and taken in concert with the multiple studies published prior to 2013 indicate the consistency and generalizability of the effect of ozone on increasing risk of asthma hospital admissions.

The mean ozone levels in most of the studies reviewed on asthma ED visits and hospitalization were predominantly below 70 ppb often with only the 75th percentile above 70 ppb (See: Table 2).

Symptoms and exacerbation

A few recent studies continue to build upon the existing studies on the relationship between ozone and asthma symptoms and exacerbation. Hasunuma et al. found that healthy children had increased cough and nasal symptoms and decreased expiratory flow with ozone exposure; interestingly, among asthmatic children only those not on controller medications showed similar increases in cough and decreased expiratory flow. Another study found that only asthmatic children using steroid medications had increased cough and shortness of breath associated with ozone. Steroid medication use in children is a marker for more severe asthma and its use may allow children to play longer outside, thus increasing their personal exposure to ozone, which in turn caused higher asthma exacerbation. In a longitudinal study of 162,752 asthmatic children in Quebec, Canada annual average ozone was associated with increased rates of severe exacerbations, resulting in ER visits and hospitalizations from 1996 to 2011. A smaller prospective study of 36 children with asthma did not find a significant association between 96-hour ozone concentration and asthma exacerbation as reported through questionnaires.

Development of asthma

A large U.S. cross-sectional study assessing asthma prevalence showed a significant risk of having asthma (OR=1.023 per ppb ozone) in adults. The Seven Northeastern Cities Study in China recruited a large cohort of 31,049 children in which a 10-ppb increase in average 8-hour maximum ozone concentration over the summer months of the prior 3 years was associated with doctor-diagnosed asthma (OR=1.1), despite median ozone levels well below 70 ppb. The data regarding incidence (development of a new case) of asthma related to ozone exposure remain somewhat mixed, though the few large cohorts that have studied this topic have found significant increases in asthma incidence with increasing ozone. In a cohort of over a million children in Quebec, summer ozone was associated with 4-6% increased risk of development of asthma, with mean ozone concentrations of 32 ppb. Some smaller cohorts in Europe and North America found no significant relationship between ozone exposure and incidence of asthma, or an inverse relationship, and a national cohort in Taiwan showed that the association between ozone exposure and risk of new-onset asthma seen only among those who carried the val105 allele glutathione-S-transferase P1 genotype. A large questionnaire-based study in the U.S. did not find any relationship between current ozone exposure (intended as a proxy for lifetime ozone exposure) and incident asthma, but this finding is difficult to interpret given the substantial risk for reporting bias and exposure misclassification. A cross-sectional study in China found an increased risk for incident asthma with 10 ppb increase in ozone (OR=1.1). Among low-income urban children enrolled in the Medicaid program
in Harris county Texas, who developed asthma, their initial date of diagnosis was more likely to occur following periods of higher short-term summer ozone levels, OR=1.05 for a 10-ppb increment in 8-hour ozone concentration over the prior 6 days.42 Thus, results from the highest-quality, large cohort studies suggest that ozone exposure at levels often below 70 ppb are possibly associated with the development of asthma. Lack of breastfeeding, overweight/obesity, and genetic factors may be susceptibility factors.

Other Respiratory Diseases

Multiple recent studies have found an increased risk of respiratory infections related to short-term ozone exposure. The odds of upper respiratory illness (URI) with a 10-ppb increment of ozone range from 0.99-1.46,11,15,43 while the odds of influenza were 1.28.44 The odds for pneumonia range from 0.99-1.1511,15 and for bronchitis 0.998-1.05.11,15,45 Similarly, studies have reported a 2.8% increase in URIs and 3% increase in pneumonias, 17 and Berhane et al. showed a decreased odds (0.31) of bronchitis with decreases in ozone concentrations. 46 Two studies—in Vietnam and Brazil—found no relationship between ozone and admissions for respiratory infections (bronchitis or pneumonia).47,48 Importantly, a recent meta-analysis of 12 studies, where exposures ranged from 13- 62 ppb, found a statistically significant increase in the risk of pneumonia (1.7%) per 10 ppb ozone.49

Some studies of very specific respiratory infections such as tuberculosis, pneumocystis carinii pneumonia among HIV patients, infantile respiratory infections, acid-fast bacillus and ozone found no or inverse associations. 50,51,52,53

In patients with cystic fibrosis, there are three recent papers relating pulmonary exacerbations to ozone exposure. There was a 6-37% increase in exacerbations with a 10-ppb increment in ozone, lagged 2 days after exposure,54,55 and pseudomonas colonization was noted to be an important effect modifier. However, long-term ozone exposure was not associated with the frequency of pulmonary exacerbations. 56

In patients with COPD, ozone seems to have less of an effect than in other respiratory diseases. There was no significant relationship seen between short-term ozone exposure and lung function57 or hospital admissions.58 For long-term exposure, there was no association between development of COPD in former asthma patients,59 and in a large longitudinal cohort in England there was no association with COPD diagnosis.60

For hospital admissions or other health care visits for respiratory diseases overall, the data are mixed. Six studies found no significant relationship with ozone exposure.61-66 However, a few studies found increases of 2-4% in respiratory admissions for a 10-ppb increase in ozone,67,68 or odds ratios of 1.04-1.08,69,70 One study noted that their results were different depending on how they summarized the ozone metrics,71 and another demonstrated variable relationships in different geographic areas.12 These may help to explain the varied results among studies, in addition to the fact that respiratory health care visits is a non-homogenous category which may mask effects for different illnesses within this category.

Ozone has not yet been clearly related to congestion or rhinitis symptoms though this has been much studied recently, with three studies showing no significant relationship,36,72,73 four studies showing a positive relationship (ORs 1.02-1.42)20,74-76 and one showing an inverse relationship (OR 0.9).77 In other respiratory effects, critically ill patients were more likely to develop acute respiratory distress syndrome
with long-term ozone exposure, OR 2.5 per 10-ppb ozone.78 Regarding lung cancer, there are three new studies: two showed no relationship between ozone and lung cancer incidence.79,80 However, a large ecologic study out of China covering 368,762 lung cancer cases found an association (OR 1.087 per 10-ppb ozone).81

**Lung function**

Several large cohort studies have found that long-term or short-term ozone is associated with decreases in lung function in healthy children (FEV1, 82-86, FVC, 82-84,87 and peak expiratory flow 29,88). Only three studies found no relationship with lung function in children, 88-90 Some studies found stronger effects of ozone on lung function in girls72 and among those carrying genetic polymorphisms. 91 In children with asthma, cohort studies have found that ozone was associated with a decrease in peak expiratory flow, 92 but no change in other lung function parameters.93 94

Recent studies in healthy adults have shown mixed results. In healthy adults, some cohort studies have found no significant relationship,95-97 though others found a 1% decrease in FEV1. 98 Controlled human exposure studies indicate that smokers and healthy nonsmokers had decreased lung function following exposure to ozone 99,100, but overweight, obese adults and healthy older adults showed an inverse relationship.35,101

Inflammation is an important component of respiratory disease and an exhaustive review of a large body of literature was carried out in the previous ISA, where there was considerable heterogeneity in responses. Epidemiological, controlled chamber studies and toxicological literature taken together supported an association between ozone and lung inflammation. Recent human studies on short-term ozone effects on airways inflammation continue to be mixed, with some studies finding an association with markers of lung inflammation102, 87, 95,101,103 and others not.95,104,105,106 No new studies of long-term pulmonary inflammatory responses in relation to ozone exposure were found.

**Summary**

In summary, there has been substantial recent research on the respiratory effects of ozone. There is additional strong evidence from the recent literature that short-term exposure to ozone is related to reduced lung function and increased respiratory infections, asthma ER visits and asthma hospitalizations. School-aged children are particularly vulnerable and the majority of the studies show stronger adverse effects of ozone at this critical stage of life.

Of the epidemiologic studies reviewed here, all but three33,52,56 have involved exposures with average or median ozone values well below the current NAAQS limit of 70 ppb, indicating ongoing risk to public health below this level.
<table>
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<tr>
<th>Paper</th>
<th>Period</th>
<th>Place</th>
<th>Ozone levels (ppb)</th>
<th>Health Outcome</th>
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<td>2008-2011</td>
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<td>Li et al 2017</td>
<td>2013-2014</td>
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<td>Max: 73</td>
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Cardiovascular and Metabolic Effects

Stroke

The recent literature on stroke as an outcome is reasonably consistent in reporting that short-term ozone exposure is associated with increased risk of hospitalizations for stroke, with multiple studies reporting significant increases (up to 3.9%) in admissions for stroke per 10 ppb ozone.\textsuperscript{107-110} A few studies which found no relationship between ozone exposure and stroke in their full population did find positive associations in subpopulations like the elderly above 75 years old,\textsuperscript{111} and particular kinds of strokes in specific racial groups: ischemic strokes in non-Hispanic whites\textsuperscript{112} and hemorrhagic stroke in African Americans.\textsuperscript{113} The relationship has even been modeled over a range of ozone values in some studies and found to be roughly linear down to as low as 15 ppb.\textsuperscript{114} An association between exposure to ozone and recurrent ischemic strokes has also been reported, with an OR of roughly 1.18, depending on the number of days lagged.\textsuperscript{115}

A stroke is an interruption of blood flow to the brain, causing paralysis, slurred speech and/or altered brain function. Two thirds of all people who have a stroke have some form of permanent disability. In the United States, a stroke happens every 40 seconds and results in one-fifth of all deaths. CDC estimates that stroke costs the U.S. economy more than $34 billion annually in direct medical costs and missed days of work.\textsuperscript{292}

Ozone concentrations have even been shown to relate to the severity of the stroke, with OR of 1.17 for severe stroke per 10 ppb ozone.\textsuperscript{116} A large meta-analysis of over 20 studies found a 2.45% increase in ischemic stroke rate per 10 ppb ozone.\textsuperscript{117} Despite the generally strong evidence for a relationship between increased ozone levels and ischemic stroke, a few studies have not supported this finding.\textsuperscript{113,118,119} Two studies have found no relationship between ozone and hemorrhagic stroke.\textsuperscript{117,120}

Arrhythmias

Recent work on the relationship between ozone exposure and arrhythmias seems to suggest a relationship in those with pre-existing cardiac disease. A small longitudinal cohort found a significant increase in ventricular tachycardia (RR 1.7) and supraventricular tachycardia (OR 1.11) related to 10-ppb ozone in coronary artery disease patients.\textsuperscript{121} Elsewhere, a retrospective study of cardiac patients who had 24-hour Holter monitoring found an increased odds of heart block (OR 1.1).\textsuperscript{122} A meta-analysis covering more than 400,000 participants in four studies (median ozone exposure 36 ppb) found a significant relationship, a 1% increase in rates of atrial fibrillation per 10 ppb ozone, and included three studies not otherwise mentioned here. This pooled odds ratio was largely driven by a very strong effect in a single study which was of patients with implanted defibrillators.\textsuperscript{123} Of the two recent studies that looked at ozone in relation to all hospitalizations for arrhythmia (regardless of patient cardiac history), one cohort and one large meta-analysis, both found no significant relationship.\textsuperscript{124,125} Thus,
the seemingly conflicting results may be related to patient inclusion criteria, with ozone having an important effect in those with pre-existing cardiac disease.

**Hypertension**

Three recent studies, including two meta-analyses, have found no significant relationship between hypertension and either short or long-term ozone exposure.\(^{117-119}\) These meta-analyses included three papers published 2012-2015\(^{126}\) and 16 papers published 2007-2017. On the other hand, four studies have found significant effects of short-term ozone exposure with admission for hypertension (OR 1.2),\(^{127}\) small increases in diastolic pressure,\(^{97,128,129}\) and small increases in systolic blood pressure.\(^{128,129}\) Long-term ozone exposure has also been associated with increased odds of developing hypertension (OR 1.13),\(^{130}\) and with increases of 0.73 mmHg in systolic blood pressure\(^{130}\) and 0.37 mmHg in diastolic blood pressure,\(^{130}\) but a decrease of 1.54 mmHg of systolic blood pressure in patients with sleep disordered breathing.\(^{131}\) One report suggests that the effects of ozone on hypertension may be more prominent in men and overweight individuals,\(^{132}\) perhaps explaining some of the variability in the study results.
In children, long-term ozone exposure has been associated with an increased odds of hypertension (OR 1.05), with stronger effects in overweight/obese children and those who were never breastfed,\textsuperscript{133,134} and short-term exposure was also associated with hypertension (OR 1.5).\textsuperscript{135} Thus, the association between hypertension and short-term ozone exposure remains an open question.

**Congestive Heart Failure**

The impact of ozone on congestive heart failure (CHF) remains unresolved. One study showed a 7.3% increase in mortality of CHF patients when they analyzed their data in a case-control fashion, but no significant changes when analyzed in a case-crossover design.\textsuperscript{136} An ecologic study in China study found no significant effect of ozone on CHF hospitalizations.\textsuperscript{137}

**Out-of-Hospital Cardiac Arrests (OHCA) and Heart Attacks**

The evidence of the effect of ozone on out of hospital cardiac arrests and heart attacks remains mixed. Most work regarding out-of-hospital cardiac arrests has shown a significant increase in OHCA with short-term ozone exposure, with ORs that range 1.02-1.4.\textsuperscript{138,139} or increases of 6.5\%.\textsuperscript{140} However, two recent studies found no significant relationship.\textsuperscript{141,142} A recent meta-analysis looking at the effect of ozone on OHCA found a pooled OR of 1.03 per 10 ppb,\textsuperscript{143} though the authors noted that there was evidence of publication bias in the included studies. Some of the differences in these studies may be due to the grouping together of all OHCA, because OHCA from different causes may be differentially affected by ozone. In fact, Rosenthal and colleagues\textsuperscript{144} recently showed that OHCA caused by MI were not related to ozone (consistent with the MI literature discussed below), but that OHCA from other causes were, with OR 1.2.

Short-term exposure to ozone may increase the risk of hospitalization for cardiovascular disease. A 10-ppb increment in ozone concentration has been associated with a 3-4% increase in hospital admissions for cardiovascular diseases.\textsuperscript{67,145} Admission for pulmonary embolism has also been associated with short-term exposure (OR 1.03).\textsuperscript{146}

A few studies have found no relationship between ozone and myocardial infarction (MI),\textsuperscript{147-151} and a few have found positive relationships with ORs of 1.2-1.4,\textsuperscript{152} or rate increases of 0.4-4\%.\textsuperscript{153,154} Other studies have actually found inverse relationships between ozone and MI.\textsuperscript{155,156} In a study that looked at hourly ozone concentration, the odds of MI increased with ozone level over the prior 72 hours, a relationship driven by effects in the cold season, a somewhat surprising finding given that many studies exclude this season from analysis due to low ambient levels.\textsuperscript{157} Ischemic heart symptoms appeared to be related to ozone levels in a Finnish study involving pharmacy records review that showed increased prescriptions for nitrates with increments of ambient ozone.\textsuperscript{158}

Other cardiovascular outcomes have been studied as well. Shields and colleagues found an association between short-term exposure to ozone and decreased heart rate variability, which worsened cardiac health.\textsuperscript{159} Qin and colleagues found increased odds of self-reported cardiovascular disease related to ozone concentrations in obese participants only.\textsuperscript{160}

**Diabetes and metabolic syndrome**
Two recent studies have found an association between ozone exposure and increased risk of developing diabetes, an important risk factor for cardiovascular disease, with HR 1.18 per 6.7-ppb ozone in African-American women,^{161} and OR 1.03-12 in an Italian study.^{162,163} Metabolic syndrome was also found to have a similar OR in relation to ozone exposure, 1.2.^{164} Intriguingly, the Italian study demonstrated an even higher odds ratio among the subgroup exposed only to levels of ozone below the WHO threshold value of 100 μ/m^3. However, other work (epidemiologic and laboratory controlled) has not shown a relationship between ozone and the processes that might lead to worsening glucose control/metabolic disorder, such as weight gain,^{165} HDL-oxidant index,^{166} leptin, insulin levels, fasting glucose, adiponectin, and resistin.^{167} One study found a decrease in HbA1c level (-1.39%) in relation to ozone.^{168} Among individuals with diabetes, one study found decreased endothelial function following ozone exposure, as measured by flow-mediated dilation.^{169} Therefore, the evidence is mixed with some epidemiologic studies reporting increased risk of diabetes and metabolic syndrome in relation to ozone exposure, but the mechanism remains poorly understood.

**Summary**

This newer literature provides evidence of the relationship between ozone and ischemic strokes, as well as some evidence for arrhythmias in those with pre-existing heart disease. Similar to our discussion of the recent respiratory literature, nearly all of the recent work on cardiovascular outcomes has been in studies with mean/median ozone levels well below 70 ppb, with the exception of one article.^{159}
Reproductive and developmental effects

Birth defects

Regarding birth outcomes, multiple studies have suggested a particular time period of risk during gestational weeks 3-12 (the primary period of organogenesis in fetal development). Lin et al.\textsuperscript{170} showed that in utero exposure to elevated ozone during weeks 5-8 there was increased risk of limb defects and polydactyly (OR for each, 1.2), and exposure in weeks 3-8 was associated with increased risk of atrial septal defect (OR 1.2).\textsuperscript{171} Exposure to ozone over the 50\textsuperscript{th} percentile (43 ppb) in the third week of gestation is associated with a nearly 3 times higher risk of pulmonary stenosis, compared to those below the 25\textsuperscript{th} percentile for ozone exposure,\textsuperscript{172} and ozone exposure in weeks 8-12 was associated with congenital heart disease, including ventricular septal defect and tetralogy of Fallot.\textsuperscript{173} Another study found an increased risk (OR 1.18) of cardiac malformations,\textsuperscript{174} and another found increased risk of craniosynostosis (OR 1.38).\textsuperscript{175} Although a few studies have found congenital anomalies related to ambient ozone, ozone concentrations in early pregnancy have not been consistently found to be related to congenital anomalies, with four studies finding no relationships for many birth defects.\textsuperscript{171,175-177}

Fertility and pregnancy complications

Recent work has also suggested an effect of ozone on fertility with reported associations between exposure and decreasing sperm counts\textsuperscript{178} and changes in ovarian responses to hormonal stimulation.\textsuperscript{179} However, ozone exposure has not been shown to affect rates of conception.\textsuperscript{180,181}

Gestational hypertension and preeclampsia are serious and sometimes life-threatening complications in pregnancy. The findings regarding the relationship of gestational hypertension with ozone exposure are somewhat mixed, with three studies showing no relationship,\textsuperscript{182-184} but three showing a relationship in the first trimester.\textsuperscript{185-187} One study also showed a slight increase in systolic blood pressure (1.3 mmHg per 10 ppb) related to ozone exposure in the second trimester, but a slight decrease (-1.9 mmHg) in the third trimester.\textsuperscript{188}

The results of several studies suggest that ozone may affect placental function. Increased risk of placenta previa was associated with first trimester ozone concentrations, OR = 1.08 per 10-ppb,\textsuperscript{189} although no relationships have been found for measures of placental volume or vascularization or placenta accreta.\textsuperscript{190} Closer to delivery, ozone levels were not associated with placental abruption,\textsuperscript{191} but were associated with biomarkers of endothelial function such as ICAM-1, VCAM-1 and endothelin-1.\textsuperscript{192}

Birth outcomes

Many studies have not found detrimental effects of ozone on fetal growth\textsuperscript{193,194} or birth weight (looking either at small for gestational age or term low birth weight).\textsuperscript{183,195-198} However, two studies have found decreases in birth weight of 13-27 g with a 10 ppb-increase in the average ozone concentration over pregnancy,\textsuperscript{199,200} and one has shown increased risk of small for gestational age with first trimester exposure, OR 1.07.\textsuperscript{201} Nascimento and colleagues\textsuperscript{202} found a significant relationship between low birth weight and ozone concentration in the final 30 or 90 days of pregnancy, OR 1.38, comparing
those roughly above and below 52 μg/m³ (or roughly 26 ppb). Two other studies also found third trimester relationships, with one finding increased risk of both small for gestational age (RR 1.16) and term low birth weight (RR 2.03), and the other showing decreases in birth weight. A geographically weighted regression among births in the U.S. state of Georgia noted that some regions seem to have positive correlations between ozone exposure and birth weight while others have negative (inverse) relationships—there are likely other factors that are modifying the relationship in different communities, which may explain the mixed results described above.

Five studies have found increases in preterm birth with whole-pregnancy ozone concentrations, with a hazard ratio (HR) for preterm birth of 1.09 per 1.5 ppb ozone; increased risk of preterm birth with whole pregnancy exposure, OR 1.08-1.10 per 10 ppb; or 4-10% increases in the risk of preterm delivery. Some studies have found the highest risk in the third trimester. Other studies show that first trimester ozone concentrations are related to increased risk of preterm delivery, OR 1.08-1.13. A study that looked at ozone concentrations by month actually found the strongest relationships for weeks 16-20 of gestation, with ORs in the range 1.08-1.21 depending on the category of prematurity. Stronger associations have been noted in asthmatic mothers, mothers who smoked, and for very preterm births. Ozone concentrations the day of and day prior to delivery were associated with premature rupture of the membranes in one study. Other studies have found that preterm birth was either less likely or not associated with ozone concentrations.

Considering fetal losses, increased ozone concentrations have been related to higher rates of spontaneous abortions and shorter time to pregnancy loss. Only one of two recent large studies found a significant relationship between ozone concentrations either over the entire pregnancy or by trimester and stillbirth, and a meta-analysis that predates these studies also found no significant relationship.

**Summary**

Although findings for reproductive effects have been mixed, all of the studies reviewed involved ozone concentrations with means or medians well below the current NAAQS of 70 ppb, suggesting the potential for harm at these levels.
Central nervous system effects

Autism

Ozone exposure during pregnancy may be a risk factor for development of autism in the child. A large case-control study (with 7,600 cases and 76,000 controls) found a 10% increase in the rate of autism diagnosis in childhood with a 10 ppb average increase in prenatal exposure.\textsuperscript{221} In a large Taiwanese cohort, childhood ozone exposure was associated with a 59% increased risk (per 10 ppb over the last year).\textsuperscript{222} Notably, that study found an exposure-response relationship where the highest risks were at highest exposures. A small case-control study also found a significant interactive effect between ozone concentration and copy-number variation (a well described genetic alteration in which sections of the genome are repeated that has been associated with autism),\textsuperscript{223} with an OR of 3.4 for a standard deviation increase of both ozone concentration and copy-number variants, suggesting that ozone may affect brain development in genetically susceptible populations. Smaller studies have looked at risks for development or severity of autism related to prenatal ozone concentrations and found no significant relationships.\textsuperscript{224-226}

Dementia

There have also been a few studies on ozone and dementia. A case-control study in Taiwan found an association between elevated ozone levels and odds of Alzheimer’s disease and vascular dementia diagnosis.\textsuperscript{227-229} However, a large cohort study in Canada found no significant relationship with new onset dementia [Hazard ratio: 0.97 (95% CI 0.94–0.98)].\textsuperscript{230} However, one study did show an 18% increase in dementia-related hospital admissions associated with increased ozone 5 days prior (per 10 ppb ozone).\textsuperscript{231}

Other

Two overlapping studies of a Taiwanese population have found increased odds of overall headache and migraine associated per 10 ppb ozone, with OR 1.04-1.43.\textsuperscript{232,233} One study also found a relationship between ozone and risk of multiple sclerosis relapse, during the warm season only, with OR 1.08 per 10 ppb.\textsuperscript{234}

Summary

In the previous ISA only one human study of ozone’s effects on the central nervous system was available, which suggested that ozone exposure was associated with poorer executive function among the elderly in the NHANES population.\textsuperscript{235} Since then there have been several studies published. Though there is heterogeneity in the effects, our review suggests that long-term exposures to elevated ozone are associated with detrimental effects on the brain, affecting the most vulnerable populations: the elderly and the developing fetus. The recent evidence indicates possible effects on autism and mental decline in the elderly. It also suggests that the effects of ozone on the brain can occur at levels below 70 ppb, as all the recently published studies included exposures well below 70 ppb.
Summary of effects of ozone on the central nervous system

<table>
<thead>
<tr>
<th>Paper</th>
<th>N</th>
<th>Outcome (subgroup)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jung et al 2013</td>
<td>49,073 Children</td>
<td>Autism (Full population)</td>
</tr>
<tr>
<td>Becerra et al 2013</td>
<td>7,421 cases/72,253 controls</td>
<td>Autism (Full population)</td>
</tr>
<tr>
<td>Volk et al 2014</td>
<td>252 cases/156 controls</td>
<td>Autism (MET genotype CC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autism (MET genotype CG/GG)</td>
</tr>
<tr>
<td>Kim et al 2017</td>
<td>158 cases/147 controls</td>
<td>Autism (Full population)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autism (Genetic CNV)</td>
</tr>
<tr>
<td>Goodrich et al 2018</td>
<td>346 cases/280 controls</td>
<td>Autism (low Folic acid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autism (High Folic acid)</td>
</tr>
<tr>
<td>Wu et al 2015</td>
<td>249 cases/497 controls</td>
<td>Alzheimer’s disease (Full population)</td>
</tr>
<tr>
<td></td>
<td>125 cases/497 controls</td>
<td>Vascular Dementia (Full population)</td>
</tr>
<tr>
<td>Jung et al 2015</td>
<td>95,690 elderly</td>
<td>Alzheimer’s disease (Full population)</td>
</tr>
<tr>
<td>Linares et al 2017</td>
<td>1175 ED visits</td>
<td>Dementia (Full population)</td>
</tr>
<tr>
<td>Chen et al 2017</td>
<td>2.1 million people</td>
<td>Incident dementia (Full Population)</td>
</tr>
</tbody>
</table>
Mortality

In the 2013 ISA, mortality effects from ozone were considered likely causal. Recent literature continues to support this assessment, including at levels far below the current 70 ppb standard.

Short term impacts

Two large ecologic time series demonstrated a significant, non-linear relationship between short-term ozone concentration and mortality that was positive above concentrations of roughly 35-40 ppb. Other recent studies found positive associations between short-term ozone exposure and mortality with an increase of 0.34-8% or an increased odds of 1.02-1.04. Reframing in terms of life-expectancy, a large study in the US found that counties with moderate population density had lower life expectancy associated with increases in ozone.

Some studies have found increased overall mortality related to ozone in particularly susceptible subpopulations, such as those with a history of MI, or during particular time periods, such as in the warm season, or the moderate-temperature season. In a meta-analysis, Bell and colleagues found an interaction between short-term ozone concentration and age with a 0.6% increase in mortality per 10 ppb ozone in younger adults and a 1.27% increase in older adults. Interactions have been reported between ozone exposure and other risks for mortality, such as temperature (both high and low) and haze (a surrogate of fine particulate matter). Liu and colleagues demonstrated that ozone mortality seems to be related to latitude in the U.S., with significant increases in mortality related to ozone in northern cities during the summer. Only two recent papers did not support a positive relationship between mortality and short-term ozone levels.

Long term impacts

The evidence for a relationship between long-term ozone concentrations and mortality is less established. Three studies have found no relationship between long-term ozone exposure and overall mortality, including a meta-analysis which covered results from 8 different cohorts with publications up until 2013. However, since then two large studies found hazard ratios of 1.02-1.08 for non-accidental deaths associated per 10 ppb ozone. This is supported by the findings of a recent study which followed 61 million elderly receiving Medicare, for over 13 years, and found a 1.1% increase in mortality per 10 ppb long-term average ozone concentration, and demonstrated that the effect of ozone on mortality remained even when they restricted their analyses to ozone concentrations <50 ppb. This study is particularly important as 1) it utilized multiple sources of information, satellite measurements, chemical transport models, land use variables as well as information from EPA ground monitors to estimate ozone exposures for the entire United States, including rural areas, where as previous studies have had to restrict their analyses to mainly urban areas, where they had good measurements or modelled data; 2) the study population in this study encompassed 96% of the overall elderly population in the United States 3) they were able to account for the joint effect of fine particulate matter and ozone together.
Looking specifically at deaths from cardiovascular causes, 10 recent papers reported a significant relationship between cardiac mortality and ozone during some portion of the year, with OR 1.01,269 HR 1.03,271 or percent increase ranging 0.6-10.0%.242,243,273 244,250,252,259,271,274 However, four studies did not find a positive relationship between ozone exposure and mortality.238,266,267,275 A study out of Canada found a significant relationship between ozone concentration and cardiovascular mortality but found that the strength of the association varied by local climate.276 Ozone exposure has specifically been related to ischemic heart disease deaths, with a HR of 1.08270 or OR 1.10268 per 10 ppb ozone.

Specifically for respiratory deaths, nine papers have reported increases related to ozone with increases of 0.65-5% per 10 ppb short-term ozone exposure,238,242,259,274,277,278 or HR of 1.03-1.12.250,269,279 Patients with acute respiratory distress syndrome were also more likely to die if they lived in high ozone pollution cities.280 Xue and colleagues found a positive relationship in the elderly (OR 1.1), but not younger adults.281 Zuniga and colleagues found a remarkably large effect with respiratory mortality increasing more than 30% in the elderly 2 months after an increase in ozone concentration.275 Four studies did not support a positive relationship between ozone and respiratory mortality.266,267,270,282

Ozone has been associated with higher rates of cancer-related deaths (HR 1.04)283 as well as specifically for ovarian cancer (HR 1.14)284 and bladder cancer.285 However, a different study found an inverse relationship between ozone exposure and deaths from some other cancer types: stomach, pancreatic and leukemia.279

**Summary**

Thus, there continues to be strong evidence for a relationship between short-term ozone concentrations and mortality and accumulating evidence for a relationship between long-term ozone exposure and mortality. Considering specific causes of death, deaths from cardiac and respiratory causes seem related to ozone levels, as are deaths from some, but not all, cancers.
Conclusions

Significant research on the adverse health effects of ozone has been published in the five years since the last ozone ISA, including both experimental human exposure studies and epidemiologic studies. The evidence reviewed here indicates that ozone significantly increases the risk of:

- **Respiratory disease**: reduced lung function, hospital admissions and emergency department visits for asthma and respiratory infections and possibly increasing rates of asthma development. School-aged children are particularly vulnerable and the majority of the studies show stronger adverse effects of ozone at this critical stage of life.
- **Cardiovascular disease**: specifically increased rates of strokes. There is also accumulating evidence supporting ozone’s effects on cardiac arrhythmia in persons with preexisting heart disease.
- **Mortality due to short-term exposure to ozone**: Evidence suggests that the effects of ozone are stronger in extreme weather (hot or cold); that women and elderly are more susceptible. New studies are adding to the evidence that long term exposure to ozone also increases rates of mortality.
- **During the last ISA there was only one epidemiological study of the effects of ozone on central nervous system.** Since then there have been several studies published, and though the emerging literature is not definitive, it suggests that long term ozone exposure could be associated with nervous system dysfunction resulting in increased risk of autism in children and possibly dementia among the elderly.

Much of the epidemiologic work has been done in populations with exposures to concentrations near or below the current NAAQS of 70 ppb ozone.

As with any continuous exposure, there are a variety of ways that ozone concentrations can be summarized, such as 24-hour averages, 8-hour averages (usually of the highest 8 hours in the day), maximum daily values, and averages of these daily statistics over longer periods of time. There is not a clearly accepted standard for how ozone exposures should be quantified in the literature, either in terms of how to summarize ozone exposure or what units to use (volume measurements such as ppb versus mass measurements like μg/m³), likely because of differences in how regulatory bodies monitor ozone in various parts of the world. The 70-ppb standard put forth by the EPA requires that the maximum 8-hour average ozone be calculated for each day, the fourth highest of those averages is taken and furthered averaged with the values across a three-year period; it is this value that must be less than 70 ppb (0.070 ppm). In the European Union, there is a non-legally binding target value for ozone of 120 μg/m³, which is intended to be the maximum allowable daily 8-hour average value (but with 25 exceptions allowed over every 3-year period).

In summary, the recently published scientific literature is remarkably robust in showing ozone health effects at levels below the current NAAQS, particularly for respiratory health. Short-term ozone exposure and respiratory disease has already been determined by EPA to be a “causal relationship”. The recent body of literature shows the adverse respiratory effects of ozone below 70 ppb in several cities and states across the United States, indicating that the current EPA standard of 70 ppb is not sufficiently...
protective of public health and should be lowered to protect public health. Furthermore, recent studies of ozone on mortality, autism and dementia suggest that long-term exposures also have adverse effects on human health. In order to fulfill the mandate to protect public health in the Clean Air Act, EPA should consider a developing a standard that encompasses a longer averaging time in order to protect the public from the adverse effects of chronic exposure and not just daily spikes in ozone levels.
Acknowledgements:

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