The Unexpected Health Effects of Air Pollution

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As noted in the 2018 Lancet Commission on pollution and health, pollution of all types (air, water, and soil) accounts for 9 million deaths per year, roughly 16% of all deaths worldwide [1]. Air pollution accounted for approximately 6.5 million of these deaths. A substantial fraction of these (4.2 million) are due to ambient air $PM_{2.5}$, which is particulate matter with mean diameter less than 2.5 μm. There is clear evidence that air pollution results in mortality due to chronic obstructive pulmonary disease (COPD), cardiovascular disease, and lung cancer [1]. In the United States, air pollution is also a leading cause of asthma exacerbations [2]. However, there is a growing body of evidence that contaminated air impacts a much broader scope of human disease.

Among those potential pollutant-related diseases listed in the Lancet report are a number of neurocognitive diseases, including autism, attention-deficit hyperactivity disorder (ADHD), and adult neurodegenerative disease. A number of investigators have reported that ambient air NO_2, O_3, particulate matter (PM) and traffic-related air particulates (TRAPs) are linked to an increased risk of autism [3-5]. The periods of exposure to ambient air pollutants associated with autism were during pregnancy and in the 1st year of life. PM, TRAPs, and NO_2 appear to have the strongest effect on autism development, while ozone was linked to a modest increase in ADHD in a small number of studies, though there remains a need for more definitive studies [3-7]. Overall, $PM_{2.5}$ seemed to be the most important pollutant associated with Autism Spectrum Disorder (ASD), and perinatal exposure appears to be the most significant exposure period.

Again, perhaps not surprisingly, there is increasing evidence that early life exposure to pollutants increases the risk of ADHD. In 2013, Newman et al observed that early life exposure to elemental carbon (a surrogate marker for $PM_{2.5}$) had increased hyperactivity scores in surveys completed by their parents when their children reached age 7 [8]. Min and Min used the National Health Insurance Service-National Sample Cohort to explore the relationship between pollutant exposure and ADHD and observed an increased risk of ADHD associated with PM_{10} and NO_2 exposure [9]. Perera et al used assessments of polycyclic aromatic hydrocarbon (PAH, a common component of PM)-DNA adducts (modifications of DNA by PAHs) in maternal and cord blood collected at delivery to estimate perinatal exposure to PAHs, and urinary levels of these adducts from children aged 3 and 5 in a cohort of Puerto Rican and Dominican children in New York. They found that high maternal adduct levels (but not those from the children) were associated with increased risk of ADHD in this cohort [10, 11].

Air pollution impacts adult neurodegenerative disease as well. Chen et al examined the incidence of dementia, Parkinson's disease, and multiple sclerosis in Toronto between 2001 and 2012 related to distance from a heavily traveled roadway [12]. They found no relationship between roadway proximity and Parkinson's disease or multiple sclerosis. However, living within 50 meters of a roadway had a hazard ratio of 1.07 for development of dementia. For urban residents this risk was 1.12. Investigators in Madrid examined the relationship between acute ambient air $PM_{2.5}$ and emergency room admissions for Alzheimer's disease and dementia, finding an increased odds ratio of 1.38 related to $PM_{2.5}$ 2 days prior to admission for Alzheimer's disease, with a weaker association with increased admissions for dementia associated with ozone

with a 5-day lag time [13, 14]. A number of earlier studies have shown relationships between ambient air $PM_{2.5}$ and decreased cognitive function in older populations.

Recent studies demonstrate that osteoporosis is affected by air pollution. This should not be too surprising, as smoking and 2nd-hand tobacco smoke exposure have long been known to contribute to bone loss and osteoporosis, likely because of increased oxidative stress and inflammation [15-18]. However, it has not been until very recently that epidemiologic data has shown that persons living in polluted areas have increased risk for acute and longitudinal markers of osteoporosis. A Taiwanese registry study showed increased risk for low bone mineral density associated with increased levels of CO and NO_2 [19]. More recently, the risk of bone fracture was reported to be higher in areas with increased ambient levels of $PM_{2.5}$ [16]. $PM_{2.5}$ was also associated with decreased parathyroid hormone in exposed persons. Carbon black exposure was associated with increased bone density loss. Likewise, living near a heavily traveled roadway has been reported to enhance bone density loss in obese or overweight Mexican-Americans in the Los Angeles region [20].

Air pollution also impacts diabetes. Lim et al reported that diabetes mortality is increased with $PM_{2.5}$ (OR = 1.19) and NO_2 (OR = 1.09), but not ozone [21]. Hernandez et al reported an association between $PM_{2.5}$ (OR = 1.10) and ozone (1.06) and incidence of diabetes mellitus using CDC data [22]. Yang et al examined the effect of PM and prevalence of diabetes in China in the 33 Communities Chinese Health Study. They found an increase in diabetes mellitus associated with $PM_{2.5}$ and PM_{10} (OR = 1.13 and 1.10, respectively) [23]. They also reported increased blood glucose associated with PM levels. Qui et al reported that long-term exposure of residents in Hong Kong to pollutants such as $PM_{2.5}$ was also associated with increased risk for type 2 diabetes mellitus [24]. Schneider et al reported in 2008 in a North Carolina-based panel study that persons with type 2 diabetes had increased endothelial dysfunction associated with $PM_{2.5}$. This effect was increased with increased glucose levels and hemoglobin A1c [25].

These all seem to be disparate health effects related to air pollution. However, each of these diseases is likely impacted by inflammation. This suggests a common mechanism by which air pollution may modulate each of these diseases. Air pollutants, including ozone and $PM_{2.5}$, have been shown to have pro-inflammatory responses, most notably activation of the innate immune system [26]. In the lung, both ozone and $PM_{2.5}$ have been shown to increase neutrophilic inflammation and inflammatory cytokines and to enhance response to inhaled allergens in persons who are sensitized to those allergens. There is also evidence that as $PM_{2.5}$ increases systemic inflammation occurs, with direct impact on cardiovascular biology and blood pressure. It has also been shown that anti-inflammatory agents reduce the impact of inhaled pollutansts on airway inflammation. As pollutants have been shown to impact systemic cardiovascular processes, it is very likely that systemic inflammation results in other pollutant-related health effects [27]. Taken together, the effect of air pollutants on the most common lung, cardiovascular, neurodevelopmental, and metabolic diseases demonstrates that air pollution is a crucial public health risk, equally important to those posed by poor food quality, infectious agents, tobacco, and alcohol use. NCMJ

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