Linkages between air pollution, COVID-19, and human health

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The What

Air Pollution vs COVID

Short-term and long-term exposure to air pollution (esp PM$_{2.5}$ and NO$_2$) may contribute to higher rates of COVID-19 infection and mortality.
Disease Similarities

Air Pollution

- **29%** of deaths from Lung Cancer
- **24%** of deaths from Stroke
- **25%** of deaths from Heart Disease
- **43%** of deaths from Lung Disease

COVID

- Asthma: 1.5x
- Hypertension: 3x
- Obesity (BMI ≥ 30): 3x
- Diabetes: 3x
- Chronic Kidney Disease: 4x
- Severe Obesity (BMI ≥ 40): 4.5x
- 2 Conditions*: 4.5x
- 3 or More Conditions*: 5x

Risk of COVID hospitalization

Stanford Medicine for Allergy & Asthma Research
Air Pollution and COVID: Widespread Inflammatory Impacts

- BNP/NT-proBNP
- Oxidative Stress
  - Uric acid
  - Myeloperoxidase
- Neurohumoral Activation
  - Renin
  - Aldosterone
- Myocardial Stretch
- Myocyte Injury
  - Cardiac troponin
- Matrix Remodeling
  - Galectin-3
- Inflammation
  - hsCRP
  - soluble ST2
- Renal Dysfunction
  - Creatinine
  - BUN
  - Cystatin C
- Others:
  - Electrolytes
  - Liver function tests
  - Thyroid function tests
  - Complete blood count
  - Iron studies
PM$_{2.5}$ is shortening lives around the world

How much air pollution shortens lives, for selected countries

- The elderly are harmed disproportionately. So with its older population, Russia has a higher loss than expected for its pollution level.
- Bangladesh faces the highest loss in life expectancy, at 1.87 years.
- Niger would gain the most, 1.45 years, if its air met the World Health Organization standard for PM$_{2.5}$ of 10 µg/m$^3$.
- With more than 18 percent of the world’s population, China’s air quality affects the most people in any single country.
- India has 10 of the world’s 20 most polluted cities.
- American lives are cut short by more than four months, on average.
- At 1.6 months, Sweden has the lowest loss of any country.
Breathing more polluted air worsen the effects of COVID-19

- China study of 120 cities and found a significant relationship between air pollution and COVID-19 infection. (Zhu, 2020)
- NO2 increased by 10 ug/m3 in the five years before the pandemic had 22% more Covid-19 cases vs PM had a 15% increase. (Tian, 2020; Wang, 2020)
- Yao et al found that air pollution was positively associated with increased COVID-19 mortality. (Yao, 2020)
- NO2 associated with the transmission ability of COVID-19. (Yao, 2021)
- The United Kingdom’s Office for National Statistics found that without controlling for ethnicity, long-term exposure to fine particulate matter could increase the risk of contracting and dying from COVID-19 by up to 7%. (United Kingdom’s Office for National Statistics, August 13, 2020)
- 1 μg/m3 PM2.5 x 9.4 more COVID-19 cases, 3 more hospital admissions, and 2.3 more deaths in Netherlands city (Cole, 2020)
- For deaths in 66 regions of Italy, Spain, France & Germany, 78% of them occurred in most polluted 5 regions (Ogen, 2020)
- Mortality in northern Italy assoc w/ the highest levels of air pollution. (Conticini, 2020)
- Petroni et al found an increase in exposure to hazardous air pollutants (HAPs) is associated with a 9% increase in COVID-19 mortality. (Environmental Research Letters, September 11, 2020)
- US long-term elevated pollution assoc with 8% increase in mortality for every 1 ug/m3 increase in PM2.5 (Wu, 2020)
- 4.6 ppb increase NO2 from traffic assoc w/ 11% increase in mortality. (Liang, 2020)
- Increase in NO2 of 8.7 ppb assoc w/ 35–60% increase in incidence & mortality in LA County (Lipsitt, 2021).
Air Pollution associated with prior epidemics and influenza

SARS
- Highly polluted area of China twice as likely to die from SARS than someone in an area with cleaner air (Cui, 2003)
- SARS epidemic - increases in particulate matter air pollution increased risks of dying from the disease (Kan, 2019)

MERS

Influenza
- Researchers have found that several viruses, including adenovirus and influenza virus, can be carried on air particles. Zhao et al found that particulate matter likely contributed to the spread of the 2015 avian influenza. (Scientific Reports, August 13, 2019)
- Chen et al found that air pollution can accelerate the spread of respiratory infections. (Environment International, January 2017)
Smoking increases respiratory infections, including COVID

Smoking doubles your risk of developing respiratory infections.
- Healthy volunteers (n=391) had 1 of 5 respiratory viruses, including a coronavirus, dropped in a liquid into their noses. Smokers were twice as likely to develop an infection (Cohen, 1993)
- Exposures to SHS and air pollution are associated with significant hypermethylation and decreased expression of IFN-γ in Teffs and Foxp3 in Tregs (Nadeau, 2012).

Smoking doubles your risk of getting sicker from COVID-19
- Smoking is associated with getting sicker with COVID-19. In the largest study of 1099 people with COVID-19, people who smoke were 2.4 times more likely to be admitted to ICU, need mechanical ventilation or dying compared to those who did not smoke (Guan, 2020).

Smoking increases ACE2 receptors.
- Goblet cells (mucus-producing) make the most ACE2 receptors.
- Smoking increases goblet cells, increasing the amount of ACE2 in the lungs (Sheltzer, 2020)
The Why

THE IMMUNE SYSTEM

Air pollution exposure impairs the immune systems ability to defend against COVID
Depth of Inhalation Varies with Size

(Ferrari, 2019)
Wildfire Smoke Inhalation: Alveolar Barrier

Krug, 2011
Alveolar Macrophages

- Interact with other lung cells (e.g. bronchial epithelial cells and dendritic cells) to try to clear the PM from the lung
- Mobilization of inflammatory cells from the bone marrow into the circulatory system
- Production of acute phase proteins by the liver
- Increase in circulating inflammatory mediators

Hiraiwa, 2013
COVID-19 Biomarkers in the Lung

SARS-CoV-2 starts its journey in the nose, mouth, or eyes and travels down to the alveoli in the lungs. Alveoli are tiny sacs of air where gas exchange occurs.

Gas Exchange
Each sac of air or alveolus is wrapped with capillaries where red blood cells release carbon dioxide (CO₂) and pick up oxygen (O₂). Two alveolar cells facilitate gas exchange: Type I cells are thin enough that the oxygen passes right through, and Type II cells secrete surfactant—a substance that lines the alveolus and prevents it from collapsing.

Viral Infection
The spike proteins covering the coronavirus bind ACE2 receptors primarily on type II alveolar cells, allowing the virus to inject its RNA. The RNA "hijacks" the cell, telling it to assemble many more copies of the virus and release them into the alveolus. The host cell is destroyed in this process and the new coronaviruses infect neighbouring cells.

Immune Response
1. After infection, Type II cells release inflammatory signals that recruit macrophages (immune cells).
2. Macrophages release cytokines that cause vasodilation, which allows more immune cells to come to the site of injury and exit the capillary.
3. Fluid accumulates inside the alveolus.
4. The fluid dilutes the surfactant which triggers the onset of alveolar collapse, decreasing gas exchange and increasing the work of breathing.
5. Neutrophils are recruited to the site of infection and release Reactive Oxygen Species (ROS) to destroy infected cells.
6. Type I and II cells are destroyed, leading to the collapse of the alveolus and causing Acute Respiratory Distress Syndrome (ARDS).
7. SIRS may lead to septic shock and multi-organ failure, which can have fatal consequences.

Image courtesy of visualcapitalist.com
SARS-CoV-2

Mononuclear Cell

Coagulation
- ↑ D-dimer
- ↑ FDP
- ↑ APTT and PT
- ↑ Platelets

Cells Inflammatory

Coagulation activation

Thrombin generation

Fibrinogen to fibrin

Activated platelet

Vascular endothelium

Fibrin clot and platelets

PAR 2

PAR 1

PAR 3

PAR 4

TLR4

Storm of cytokines
- ↑ IL-6, IL-2, IL-4, TNFα

Pro-inflammatory cytokines

Impairment of natural anticoagulant pathways

Shut down of fibrinolysis
Cutting Edge Technology

1. Isolate PBMCs
2. Stain PBMCs with metal-tagged antibodies
3. CyTOF

Data Analysis

Intensity

Mass of Metal
Immune Cell Plot
Air pollution exposure is linked with methylation of immunoregulatory genes, altered immune cell profiles, and increased blood pressure in children. (Prunicki, 2021).
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