AIR POLLUTION AND HEALTH: NOVEL INSIGHTS ON BLACK CARBON TOXICITY AND AIR POLLUTION IN THE CORONAVIRUS DISEASE 2019 PANDEMIC

by
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ACKNOWLEDGEMENTS

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Dr. Weiss also introduced me to Dr. Charles Steenbergen, from Pathology, who exhibited an equally open mind and enthusiasm for exploring environmental toxicology research despite its deviation from his usual academic activities. Dr. Steenbergen connected me with the supply of tissue samples used to conduct the original research in this capstone, offered his expert insight to interpret the findings, and generously took the time to review and comment on the final capstone product in its entirety.

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Dr. Castillo specifically encouraged me to expand the scope of this project to include the relationship of air pollutants to population health in the context of the ongoing coronavirus disease 2019 (COVID-19) pandemic. This aspect of the project presented the opportunity to highlight disparities in air quality and COVID-19 outcomes, which was ultimately the most relevant and timely component of the project. His input truly elevated this capstone and I am grateful for his feedback and direction.

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EXECUTIVE SUMMARY

Black carbon (BC) is a pollutant generated by incomplete combustion processes. It is highly representative of traffic emissions in urban areas, and is always associated with other chemicals of varying toxicity in the atmosphere. Its accumulation has been associated with a number of adverse health effects, including premature mortality, pulmonary and cardiovascular diseases, abnormal pulmonary and cognitive development in children, adverse perinatal outcomes, and epigenetic and genetic derangements.

This capstone contributes to the understanding of BC toxicity by demonstrating that BC accumulates in human extrapulmonary tissue. The size and distribution of particles recovered from organs offer specific insights into BC toxicokinetics and lay the groundwork for future toxicology studies.

In this context, the United Nations Environment Programme recommendations for BC pollution mitigation and current methods for BC emission surveillance are reviewed. International and local disparities in resources for air quality surveillance are highlighted as well as opportunities to reduce said disparities for the benefit of affected populations.

Lastly, this capstone summarizes the current understanding of the bidirectional relationship between the recent coronavirus disease 2019 (COVID-19) pandemic and air pollution. Specifically, the dramatic decrease in global air pollution documented by satellite since the outbreak of this disease is described along with an original analysis on recent trends in air pollutant levels in New York City. Data from New York City are also utilized to supplement recent discussions on the suspected effect of chronic exposure to specific air pollutants on morbidity and mortality associated with COVID-19 infection.

CAPSTONE OBJECTIVES

The goal of this capstone is to update and summarize known health risks associated with air pollution to highlight the importance of mitigation and equity in resources for surveillance. The specific objectives are as follows:

1) Report original research documenting black carbon accumulation in human extrapulmonary organs
2) Review current recommended strategies for mitigation of black carbon pollution from the United Nations Environment Programme
3) Review and compare current methods and disparities in resources for air pollution surveillance with an emphasis on black carbon pollution
4) Compare data from New York City with findings from published literature on the bidirectional relationship between air pollution and the coronavirus disease 2019 pandemic

BLACK CARBON AIR POLLUTION AND HEALTH: AN OVERVIEW

Black carbon pollution (BCP) is generated primarily as a product of incomplete combustion from burning of fossil fuels, residential wood and coal, oil and coal from power stations, agricultural wastes, and forest and vegetation.[1,2] In the atmosphere, BCP particles coagulate, aggregate and associate with other chemicals of varying toxicities, including metals, metalloids, polyaromatic hydrocarbons, and bacterial endotoxin.[3-6] Toxicity of inhaled BCP is generally attributed to particles 2.5 μm in greatest dimension or smaller being inhaled to lung alveoli and particles 100 nm or smaller translocating through the alveoli to the bloodstream.[7-11] BCP particles that remain in the lung can form chain-

aggregates of carbon particles and other pollutants and accumulate in airway macrophages, bronchial epithelial cells, and pulmonary fibroblasts.[12-14] In animal models, particles 100 nm or smaller also accumulate in the nasal mucosa and translocate along the olfactory nerve to enter the olfactory bulb of the brain.[15] To date, anatomic studies in humans have confirm BCP accumulates in the lung and circulates systemically to accumulate on the fetal side of the placenta and in excreted urine.[74-75, 77-78]

Epidemiologic studies independently associate BCP with all-cause mortality, mortality from pulmonary and cardiovascular causes, and morbidity involving several physiologic systems. In the United States, 14,000 deaths and hundreds of thousands of illness cases are estimated to result from BCP exposure on an annual basis.[21]

Pulmonary morbidity associated with BCP includes hospitalizations for any respiratory illness, abnormal pulmonary development, increased asthma prevalence and severity, and overall decreased pulmonary function.[16, 20, 22-47] Associated cardiovascular morbidity includes hospitalizations for any cardiac illness, ischemic heart disease, autonomic dysfunction, arrhythmias, and hypertension linked to underlying inflammation, plaque formation, endothelial dysfunction, and platelet activation.[11,23,48-60] Adverse neurocognitive outcomes associated with BCP include impaired cognitive development in children and increased cognitive decline in the elderly.[61-63] Epigenetic markers of biologic aging and carcinogenetic risk are also associated with BCP.[64-66] Lastly, prenatal exposure to BCP is independently associated with reduced birth weight and increased systolic blood pressure at birth.[67-68] Evidence suggests that obesity and specific genetic profiles act as effect

modifiers for several adverse health effects associated with BCP.[38,52,57,67,69-73] A complete review of BCP toxicity is included in *Appendix A*.

ORIGINAL RESEARCH INVESTIGATING PATTERNS OF BLACK CARBON ACCUMULATION IN EXTRAPULMONARY HUMAN TISSUES

Based on the known toxicokinetics of BCP particles in the human body, we postulated that particles are likely to accumulate in extrapulmonary organs, including the hilar lymph nodes, heart, and spleen. Within this framework, we applied a protocol recently validated for extraction of chemically inert microplastic particles from fish tissue to investigate the characteristics of particles that could be recovered from post-mortem human tissue.[79] This protocol was submitted to the Johns Hopkins Bloomberg School of Public Health Institutional Review Board Office and determined not to qualify as human subjects research and to not require IRB review or oversight. Myocardial and splenic specimens were collected from three de-identified sources post-mortem. Hilar lymph nodes were also collected from two of these sources. No microplastic particles were visualized, but extraction of black carbon particles from the hilar lymph nodes, myocardium, and spleens from each source (referred to herein as Source #1, Source #2, and Source #3) was confirmed. Results are reported by carbon load and particle size, stratified both by organ type and by individual. Trends in observed particle size and concentrations across tissue categories are suggestive of the mechanisms by which black carbon circulates in the human body and accumulates in extrapulmonary sites.

Methods

Chemicals and other materials

Materials included potassium hydroxide (KOH) and sodium iodide (NaI). Solutions of KOH (10% w/v), and 4.4 M NaI were prepared by dissolving powder/pellets in reverse osmosis-grade water. Filter papers were supplied by Whatman Inc. (Grade 1 and 540 hardened ashless and Grade 1, Florham Park, MI).

Tissue Preparation and Digestion

Post-mortem tissue samples were obtained from the Johns Hopkins Department of Pathology. Samples were received in polypropylene tubes containing 10% neutral buffered formalin. Samples were removed from formalin with forceps and rinsed three times with reverse osmosis-grade water before being transferred to a glass plate to be weighed on a Metler analytical scale. Tissue was manually cut with razor blades to fragments less than 0.5 cm in greatest dimension to enhance homogenization. 10% *w/v* KOH was added to the tissue at 10cc/g tissue. KOH solutions containing tissue samples were then homogenized with a Polytron homogenizer at medium speed for five minutes. The homogenate was covered with paraffin wax and transferred to a 40 °C water bath for 48-72 hours.

Removal of Digestion-resistant Particles

After 48-72 hours, the homogenates were filtered over a Whatman Grade 540 membrane (8 μm pore size). Filter membranes were transferred to beakers containing 10mL 4.4 M NaI solution. To dislodge particles bound to the filter, beakers were sonicated at 50 Hz for 5 minutes and agitated on an orbital shaker (200 rpm) for five minutes. Particles were

isolated by centrifugation at 500 x g for two minutes. The supernatant was collected in a collection bottle, and remaining pellets were re-suspended in the NaI solution, sonicated, agitated, and centrifuged. This re-suspension procedure was repeated twice. Collected supernatants were filtered over Whatman Grade 540 filter membranes and transferred to glass petri dishes with lids. Covered petri dishes containing filter membranes were vacuum-dried at 25-30 mmHg at 40 °C for 45-60 minutes. After drying, covered petri dishes were sealed with paraffin wax for transport for microscopic examination and Raman analysis. The processes for tissue digestion and removal of digestion-resistant particles are represented schematically in Figure 1.[79]

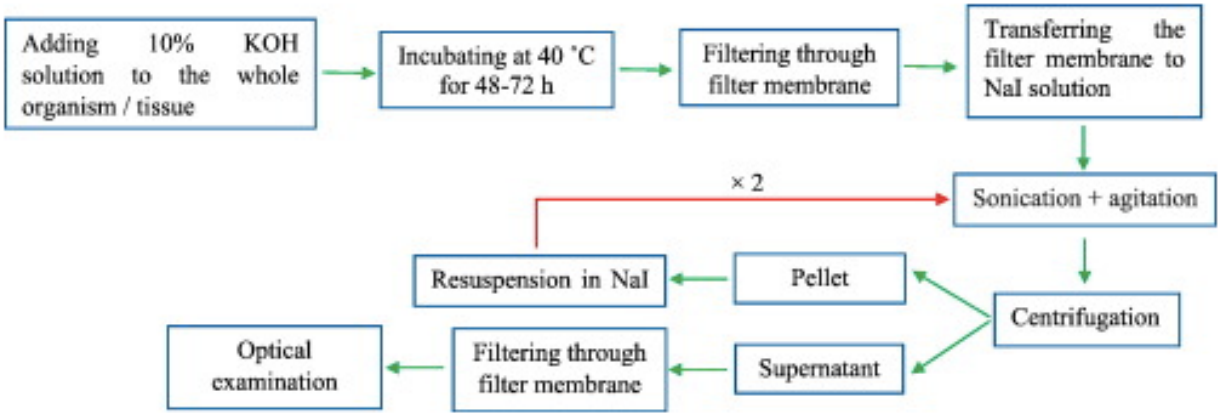

Figure 1. Flow diagram of the protocol to extract inert particles from tissue. Source: Karami et al., 2017.

Microscopy and Raman Analysis

An Olympus microscope equipped with an XY stage with 0.05 μm minimum incremental movement was used to scan filter papers for evidence of accumulation of inert particles, including black carbon and microplastics. Because microplastic particles were not

identifiable under the microscope against the white filter paper, the focus of the study became identification and characterization of recovered black carbon particles. Once identified, the greatest dimensions of suspected black carbon particles were measured and recorded. The Olympus microscope was attached to the Raman spectrometer T64000 Horiba Jobin Yvone equipped with a liquid nitrogen cooled CCD detector. To evaluate the molecular composition of isolated particles, Raman analysis was performed and recorded over a range of 100 to 2000 cm− 1. A 514.5 nm line of Ar+-Kr+ laser was used for excitation. A 2 μm laser probe allowed for probing of particles 2 μm in largest dimension or larger. Spectra of carbon particles were identified by comparison to literature on Raman spectra of various forms of carbon.[80] To minimize bias, researchers conducting microscopy and Raman analysis were blinded as to the source of the particles being characterized.

Prevention of Contamination and Procedural Controls

To prevent contamination, working surface areas were covered with aluminum foil thoroughly cleaned with KIMWIPES (Kimberly-Clark Worldwide, Inc., Irving, TX) soaked in distilled water prior to work. All the solvents were filtered over a Whatman Grade 1 filter membrane (11 μm pore size) prior to use. All glassware was cleaned with commercial dishwashing liquid and rinsed with reverse osmosis-grade water. Procedures were carried out under a flow cabinet to prevent potential contamination with airborne pollutants. When not under a flow cabinet, solvent containers were covered with paraffin wax and petri dishes were covered with glass lids and paraffin wax.

Between processing of samples, all equipment was cleaned with commercial dishwashing liquid and rinsed three times with reverse osmosis-grade water. The procedural control was a 40 mL KOH blank processed in parallel with tissue samples.

Results

Recovery and Confirmation of Black Carbon Particles

Black carbon particles were confirmed on all filter membranes exposed to products of digested tissue samples and the KOH procedural blank. An image of an extracted particle and the associated Raman analysis are pictured in Figure 2.

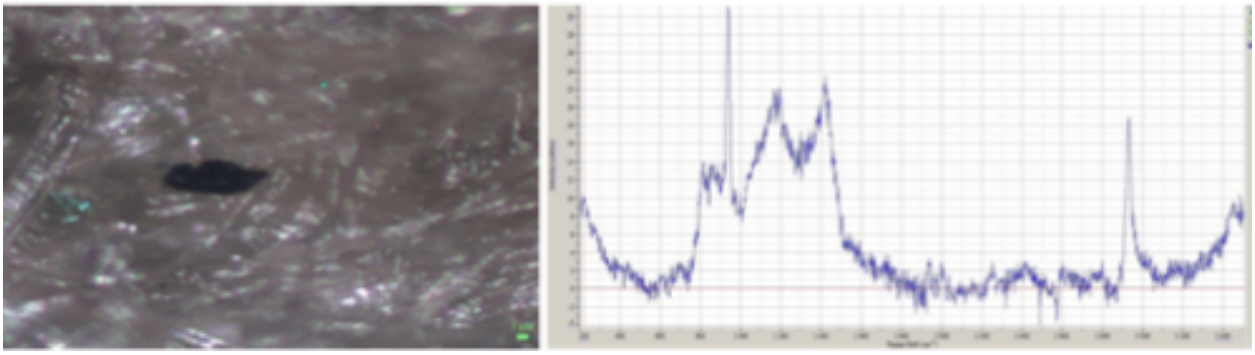

Figure 2. Microscopic image and associated Raman spectrum of carbon particle extracted from the hilar lymph node of Source 1.

Intravariability and Intervariability of Black Carbon Concentrations

Tissue samples ranged from 3.3g to 8.3g in weight. To evaluate the carbon load intravariability (different organ tissues from the same individual) and intervariability (same organ tissues from different individuals), results for tissue specimens are reported as the total number of black carbon particles accumulated on filter membranes per gram of

tissue processed (Figure 3A). Because this calculation was not possible for the procedural blank, experimental samples were compared to the procedural blank by total particle count per 40 mL volume (Figure 3B). Overall, specimens from Source #3 exhibited a greater carbon load compared with like specimens from Source #2 and Source #1. Due to the lower particle concentration in the spleen sample from Source #1, comparisons of black carbon loads were not consistent between Source #2 and Source #1. Within individuals, the carbon load of hilar lymph nodes was consistently greater than myocardial and splenic loads, and myocardial loads were consistently greater than those from the spleen.

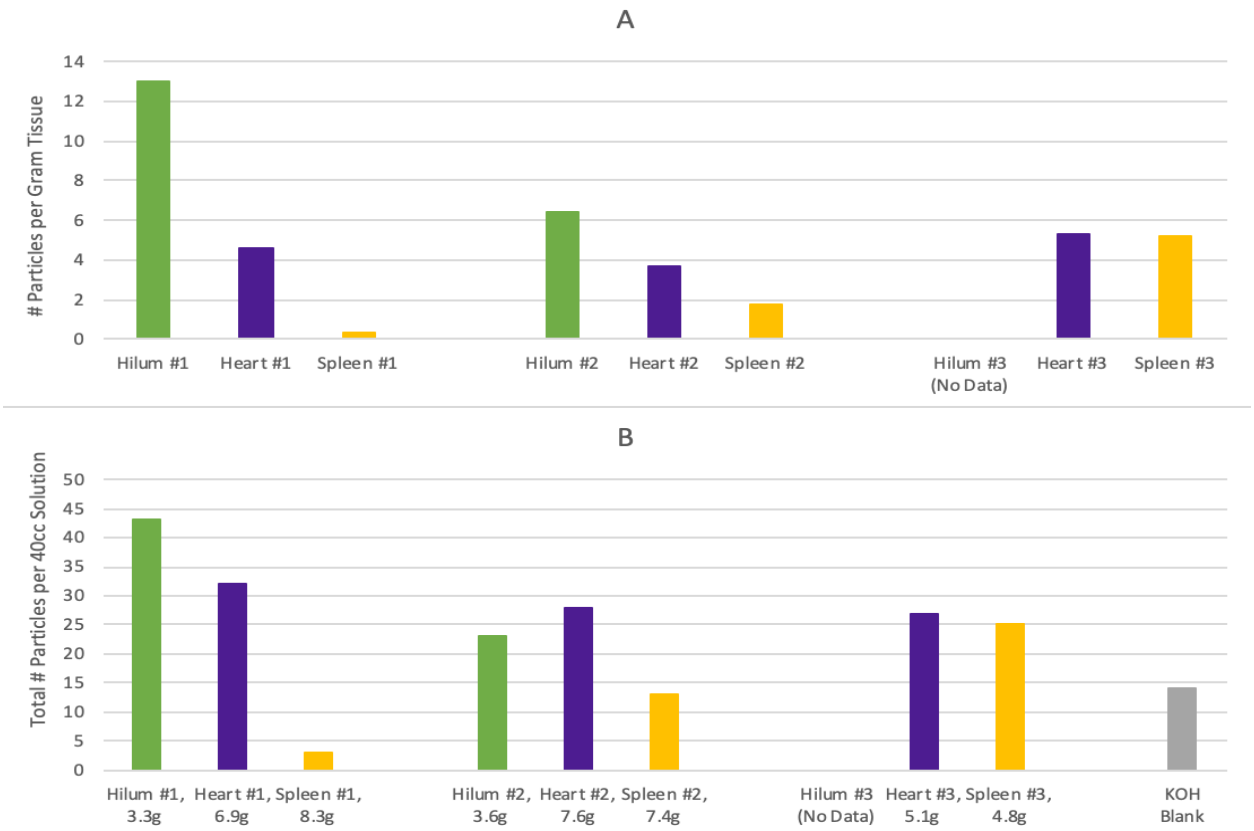

Figure 3. Black carbon loads of tissue specimens and procedural blank. A) Number of accumulated black carbon particles per gram of tissue by organ and source individual. B) Total number of carbon particles per 40 mL solution comparing experimental samples with the procedural blank.

Intravariability and Intervariability of Carbon Particle Size

From the size determination of identified particles, it is clear large black carbon particles can be found in the human heart, spleen, and hilar lymph nodes (Figure 4). Recovered particles ranged from 2 μm to 45 μm in greatest dimension across sources and organ type. Within sources, particles recovered from the spleen were on average consistently larger than those recovered from the myocardium. No other discernable pattern could be appreciated within and between sources with regard to particle size distribution.

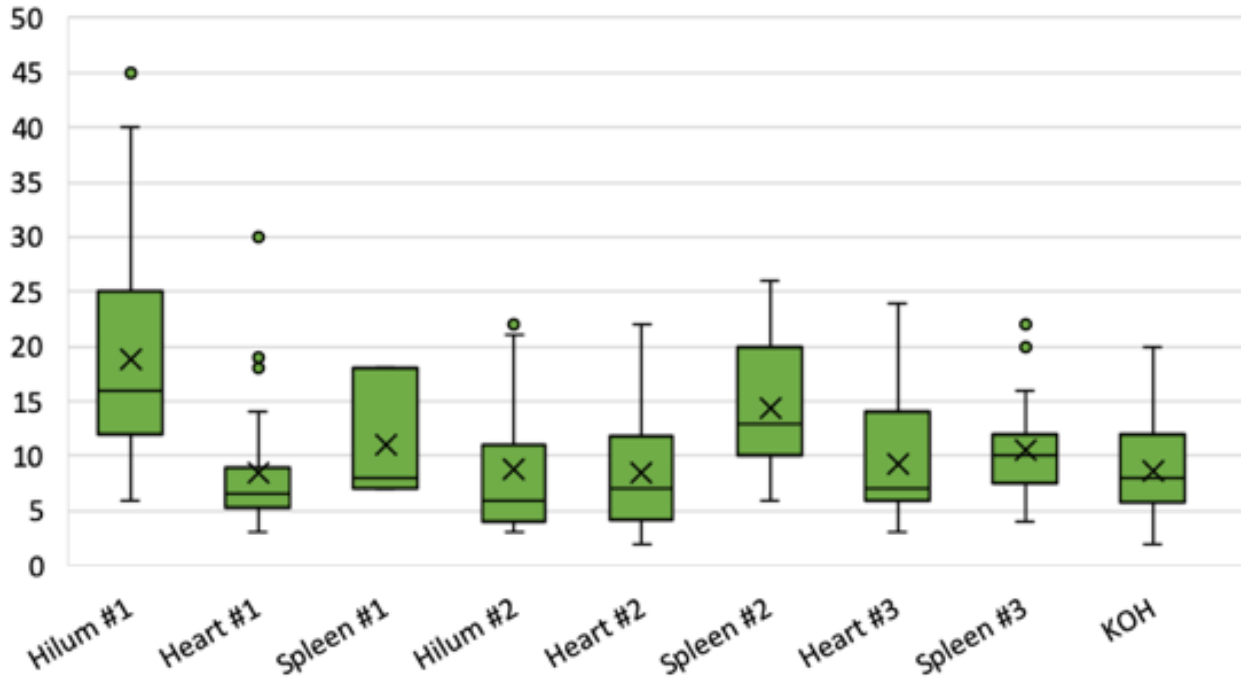

Figure 4. Box plot representing black carbon particle size in largest dimension in tissue specimens and the KOH procedural blank.

Discussion

In the human body, black carbon particles are known to be phagocytosed by macrophages and bronchial epithelial cells and to translocate through alveoli and nervous tissue. We utilized a validated protocol for recovery of inert particles to screen small samples of fixed post-mortem human tissue for accumulation of black carbon.[79] Black carbon particles were visually identified in all tissue samples tested and confirmed by Raman spectroscopy. The size of recovered particles and their patterns of distribution were analyzed to generate hypotheses to explain how black carbon migrates to extrapulmonary sites in the human body (Figure 2). Because of the variability of particle toxicokinetics observed between species, results from this study are interpreted based on what is specifically known of particle uptake and movement in humans and human cells.[81,82]

Comments on Intravariability and Intervariability of Black Carbon Particle Concentrations Recovered from Extrapulmonary Sites

With the exception of the small particle count recovered from the spleen of Source #1, the consistency of the pattern of relative concentrations of microparticles between sources and organs is validating for this technique. Within each source, the concentration of particles recovered from hilar lymph nodes exceeded that of particles recovered from the heart, which exceeded the concentration of particles from the spleen. These findings suggest the possibility that particles phagocytosed by macrophages are more likely to become trapped in the myocardium compared with the spleen after draining through the lymphatic system, the thoracic duct, and the venous circulation.

Comments on Size of Black Carbon Particles Recovered from Extrapulmonary Sites

Recovered black carbon particles measured up to 45 μm in greatest dimension, which is considerably larger than particles previously observed to translocate through alveoli.[8-11] Therefore, we infer that recovered particles migrate to extrapulmonary sites after phagocytosis by macrophages. However, the specific anatomic site at which these particles are phagocytosed or the size of particles prior to phagocytosis cannot be definitively inferred.

One source of ambiguity in interpreting these findings is that black carbon particles can exist as primary particles or aggregate particles comprising primary particles compacted by crystallization. They can also exist as agglomerate particles comprising primary particles joined by weak physical associations, although these associations are easily broken in aqueous solutions.[83] Thus, black carbon particles accumulated on filter membranes represented either primary particles or aggregate particles that formed within tissues or phagocytic cells. Tissue fixation prior to digestion may have strengthened aggregate crystals and contributed to the increased average size of particles recovered after processing in aqueous solutions.

The majority of studies investigating particle toxicokinetics of micro- and nanoparticles after inhalation in humans utilize iron oxide as the exposure material.[84-89] Based on these studies it is understood that after inhalation, primary particles distribute in airways according to their size. Specifically, iron oxide particles over 2-4 μm in greatest dimension are more likely to distribute to more proximal bronchi, bronchioles, and upper airways compared with smaller particles that more readily distribute to alveoli.[84,90] Approximately

half of particles that deposit in ciliated airways will be undergo mucociliary clearance within 24 hours, by which particles are cleared from the lung, swallowed, and potentially exposed to phagocytic cells in gut-associated lymphoid tissue.[84,88,91] Clearance of particles remaining in both the alveoli and bronchial airways takes at least several months and is thought to be mediated primarily by alveolar and bronchial macrophages.[84,85,92-94] Particles that translocate to bronchial epithelial cells may also eventually be phagocytosed and cleared by interstitial macrophages.[81]

Although the upper limit of the size of particles that are phagocytosed by airway macrophages in vivo has not been defined, murine macrophages in vitro can phagocytose carbon particles up to 20 μm in greatest dimension.[95] In addition, in human studies, most macrophages are observed to phagocytose more than one particle, in one case accumulating up to 72 microparticles before clearing the airway.[89] Thus, based on review of scientific literature, the possibility exists for most recovered particles in the study to have been primary particles upon inhalation or ingestion or to have aggregated within phagocytic cells.

Limitations of this Study

Although the results of this study offer new insights on the toxicokinetics of black carbon particles of in the human body, several limitations of this study are noted. Most importantly, the number of particles recovered from the procedural KOH blank was higher than expected and likely indicates the need for a more powerful hood or stronger environmental controls during microscopy or Raman analysis for future investigations. Second, due to the difficulties associated with manually cutting fixed tissue to the

appropriate dimensions, the tissue samples from which carbon particles were extracted were relatively small. This limited the data that was analyzed to support the conclusions of this study. In addition, the lower than expected concentration of particles derived from the spleen of Source #1 suggests the possibility the filter membrane may have been compromised.

There was no standardization of tissue samples chosen for analysis to account for possible regional differences of particle concentrations within organs. Lastly, the 8 μm pore size of the filter membranes may have biased the calculations of particle concentrations and average particle sizes toward larger particles.

Future Directions

Based on this work, a number of opportunities exist for future study. First, an experimental protocol that recovers black carbon particles placed in vivo would be useful for validating the use of these methods for the recovery of black carbon. Also, histologic examination of tissue pathology slides will be important to verify reported findings and to offer additional detail regarding intracellular and extracellular distribution of black carbon particles at extrapulmonary sites. Conducting studies using larger sample sizes, samples from additional extrapulmonary sites, and comparing results between fixed and unfixed tissue could also be a next step. Because the efficiency of short- and long-term clearance of inhaled particles is known to be affected by a number of pulmonary diseases and smoking history, conducting a study using tissue from sources with known medical and tobacco histories in addition to known geographic and tattoo histories would be useful.[87,92] Lastly, conducting a study using filter membranes with a smaller pore size might yield results that

more accurately reflect in vivo particle accumulation and allow for more robust statistical analysis.

BLACK CARBON POLLUTION MITIGATION AND SURVEILLANCE

As described, the health risks associated with BCP are significant both in number and in their measured associations. Black carbon is also a short-lived climate pollutant with anywhere from 460-1500 times the warming effect of carbon dioxide. Because BCP only exists in the atmosphere for 4-12 days, emission reductions immediately benefit both the climate and public health.[2,96]

Black Carbon Mitigation

Without intervention, BCP emissions on a global scale are unlikely to decrease. Improvements in standards for road traffic and replacement of biofuels in the Americas, Europe, and East Asia are currently offset by increases in emissions in Africa and West Asia.[2] Of the 6.6 million tons of BCP emitted into the atmosphere in 2015, 88% was attributable to open biomass burning and residential solid fuel combustion in Asia, Africa, and Latin America. 58% of global BCP is specifically attributable to household cooking and heating.[97]

BCP mitigation requires interventions that are country- and region-specific. It also requires regional and inter-regional sharing of scientific knowledge, technology transfer, monitoring, and policy and capacity development.[2] Based on outcomes predicted by the Greenhouse Gas – Air Pollution Interactions and Synergies (GAINS) model created by the International Institute for Applied Systems Analysis, the United Nations Environment Programme (UNEP) has specific recommendations for the reduction of BCP. These

recommendations would also lead to reductions in other air pollutants, including total $PM_{2.5}$, carbon monoxide, and organic carbon.[2,98]

Specific measures recommended by UNEP to reduce BCP are stratified by the societal sector to which they apply. For transportation, elimination of high-emitting diesel vehicles and filtering of diesel particles from remaining diesel vehicles is recommended. For private residences, particularly in low- and middle-income countries, replacement of coal by coal briquettes in cooking and heating stoves, replacement of conventional wood with recycled wood or sawdust in pellet stoves and boilers, and introduction of stoves utilizing clean-burning biomass or modern fuels are all recommended. Industries are requested to replace traditional brick kilns and coke ovens with modern alternatives and to adopt end-of-pipe abatement measures to reduce emissions. The banning of open field burning of agricultural waste is also recommended for farmers.[2] Additional recommendations include eliminating use of kerosene lamps and the practice of waste gas flaring during extraction and processing of crude oil and natural gas.[96]

Altogether, these interventions could reduce BCP by as much as 80% by 2030.[2,97] They are also projected to prevent 0.7 – 4.6 million premature deaths annually by 2030, with 80% of the mortality benefit localized to Asia.[2]

Air Quality Surveillance

Surveillance and monitoring is vital for international collaboration and capacity building for BCP mitigation. A number of methods have been widely applied for the monitoring of BCP and other pollutants. Broad categories of air quality surveillance include regulatory and non-regulatory direct air quality measurement, air quality modeling, and emission

inventories based on modeling data. An overview of each of these categories is described here.

Regulatory Air Quality Measurement

Regulatory monitoring of BCP and other air pollutants exists for the purpose of determining if levels comply with regional regulations.[99] In the United States, the Environmental Protection Agency (EPA) and state agencies support a network of air quality monitors placed near ground-level that measure $PM_{2.5}$, but not BCP specifically, to track compliance with National Ambient Air Quality Standards.[100,101] This monitoring network is relatively sparse, comprising approximately 1200 monitors for the entire country. Monitors are also limited in their ability to measure sharp spatial variations in pollutant levels at the neighborhood scale that reflect environmental injustices and environmental racism, in part because they are designed to be placed far from major roadways. They are also expensive to operate and maintain compared with non-regulatory methods.[99]

Worldwide, significant disparities exist with regard to infrastructure for air quality monitoring. Although regulatory monitors in the United States are reported to be inadequately and inequitably distributed, the United States has one of the most concentrated air quality monitoring systems in the world.[99,102] Chile has a comparable concentration of monitors relative to population size. India, Russia, Brazil and South America have significantly lower coverage, while many cities in low- and middle-income countries have no air quality monitoring at all. Extending monitoring to these cities, particularly where health care cannot adequately mitigate the negative health effects of air pollution, is urgently needed.[102]

Non-regulatory Air Quality Measurement

To better assess intra-urban spatial distribution of air pollutants to the neighborhood level, some cities set up additional air quality monitors aside from those required by regulatory agencies. An example of these non-regulatory direct air quality monitoring systems is the New York City Department of Health & Mental Hygiene's New York City Community Air Survey (NYCCAS). NYCCAS was set up in 2008 to supplement the 21 state-operated regulatory monitoring stations located in the New York Metropolitan Area. The NYCCAS network is the largest ongoing urban air monitoring network specific to any city in the United States. In brief, NYCCAS monitors collect cumulative samples over a two-week period once per season. They are present in approximately 100 locations in New York City randomly selected after stratification for building and traffic density.[103] NYCCAS derives BCP levels based on reflectometry of collected $PM_{2.5}$ filters. Its monitors are less expensive to operate than those set up by the EPA, but still more costly and technologically complicated than other sensors on the market.[99,104] Non-regulatory measurements are also more susceptible to errors involving statistical noise and systemic biases than regulatory measurements.[99]

Air Quality Modeling

In the absence of monitors that directly measure air pollutants, modeling can be used to estimate $PM_{2.5}$ levels. Examples of pollution models used in epidemiology include more basic proximity-based assessments (e.g. distance to major roadways), statistical interpolation between sparse environmental monitors, land use regression models, atmospheric air dispersion and chemical transport models, integrated emission-

meteorological models based on satellite data, and models that are a hybrid of these approaches.[105] Several of these methods have fallen out of favor due to advances in technology and data availability. Chemical transport and air dispersion models in particular are expensive and require a large amount of input data to be supported.[106] Specific overviews of land use regression and satellite modeling are provided here.

Land Use Regression

Land use regression (LUR) utilizes input data including land use information, traffic volume, road types, elevation, and population density to estimate ambient $PM_{2.5}$ concentrations. Although LUR can yield exposure assessments at relatively finer spatial resolutions compared with other models, it is generally limited in temporal resolution due to time-invariant land use parameters. LUR has been used in isolation to demonstrate meaningful associations between air pollution and public health outcomes, but is increasingly incorporated into hybrid models applied to study of air pollution in urban settings with increased spatial variability of air pollutants.[99,107]

Satellite Modeling

Since the 1990s, models incorporating satellite data have been used to quantify tropospheric air pollution with increasing temporal and spatial resolution.[105] The key measurement integrated into satellite-based models is the aerosol optical depth (AOD), a light-based measurement estimating the amount of aerosol in the atmosphere as a proxy for $PM_{2.5}$. One commonly used source of satellite data is the MODerate resolution Imaging Spectroradiometer (MODIS) instrument that comprises equipment placed on two satellites. This instrument provides a daily data set for all locations on earth with moderate spatial

resolution.[108] The Multi-Angle Implementation of Atmospheric Correction (MAIAC) algorithm developed for MODIS improved spatial resolution of data to 1 km.[99,105,109]

Although models incorporating satellite data can be used in isolation to assess $PM_{2.5}$ pollution where surface sensors are limited or not available, the quality of assessments generally improves with increasing correlation with near-ground measurements.[99,105] Satellite data are therefore commonly used as components of hybrid models that may also include LUR, regulatory measurements, non-regulatory measurements, or meteorological parameters that enhance spatial or temporal resolution.[99]

Specific strengths of MODIS data for $PM_{2.5}$ analyses are public availability, ease of attainment, and the frequency of its measurement. However, these data do not allow for quantification of aerosol by size or composition. They also are not representative of air quality at breathing level. Satellite data are also masked by cloudy weather.[105]

Emission Inventories

Another method for monitoring BCP is calculation of emission inventories to estimate the amount of combustion of sources of BCP. Emission inventories account for the amount of black carbon emitted into the atmosphere by utilizing complex models to estimate emission factors, defined as mass of pollutant emitted per unit of activity within the relevant time span. Emission factors are then multiplied by activity data, quantitative measures of events that lead to emission, to calculate the end emission inventory product. Although technologically and politically complicated, emission inventories are valuable assessments upon which global coalitions and scientific communities base policies and initiatives for pollution mitigation. For example, the United Nations Environment

Programme – World Meteorological Organization report that prioritized key BCP mitigation strategies was based on data from the IIASA GAINS model.[98] These data have since been applied globally in the OECD study of the economic impacts of air pollution.[96,110]

Effective emission inventories require an accurate appraisal of all emission factors and activity data. However, factors that are representative of BCP emissions in low- and middle-income countries in Asia, Latin America, and Africa are often poorly characterized or excluded from available models, leading to significant uncertainties in emission inventory calculations for those regions. Commonly mischaracterized factors include open-burning of municipal solid waste, domestic biomass burning for traditional cookstoves and ovens, open-burning of crop residues, use of traditional kilns for brick production, burning of forests and savanna, and charcoal production.[96]

Uncertainties specifically associated with measurement of BCP emission factors exceed uncertainties associated with estimating emission of other pollutants. Globally, there is currently a need for authoritative and systematic methods of appraisal of emission factors and activity data related to BCP to produce consistent and comparable emission inventories on which to base policy and strategy.[96]

AIR POLLUTION AND THE CORONAVIRUS 2019 (COVID-19) OUTBREAK

Current literature is suggestive of a bidirectional relationship between air pollution and the COVID-19 pandemic, whereby the pandemic has resulted in reduced levels of air pollutants while chronic exposure to air pollutants may worsen health outcomes associated with COVID-19 infection. Although studies associating COVID-19 with air pollution are not currently specific to BCP, the relationship of the recent pandemic with air pollution levels

warrants exploration. The significant percentage of the BCP component in air pollution in urban areas and the correlation of its levels with levels of other criteria air pollutants relevant to the COVID-19 pandemic makes this topic especially relevant and timely.[1,2,111]

Effects of Coronavirus on Ambient Air Pollution Levels

Reductions in Nitrogen Dioxide Estimates Based on Satellite Data

Since the onset of the COVID-19 pandemic, satellite images have consistently detected reductions in atmospheric nitrogen dioxide (NO_2), a pollutant highly correlated with the burning of fossil fuels and an overall indicator of human activity.[112] In late January, Chinese authorities shut down transportation connecting the Wuhan province with the rest of the country and local Wuhan businesses in response to the emerging pandemic. By February, Tropospheric Monitoring Instrument (TROPOMI) satellite data were able to detect a 10-30% decrease in NO_2 over several Chinese provinces compared with average data from 2005-2019. However, these findings were likely partially confounded by recent air pollution restrictions in China.[113] TROPOMI data revealed similar findings over Northern Italy by early March.[114]

Over metropolitan areas of the Northeastern United States, NASA satellite measurements detected reductions in NO_2 after widespread lockdowns and shelter-in-place orders were instituted for the region. These estimates were derived using Ozone Monitoring Instrument (OMI) satellite data. They were the lowest for the month of March since OMI was implemented in 2005, and reduced approximately 30% compared with average levels from 2015-2019.[112] Vertical comparison images of all referenced satellite data are presented in Figure 5.

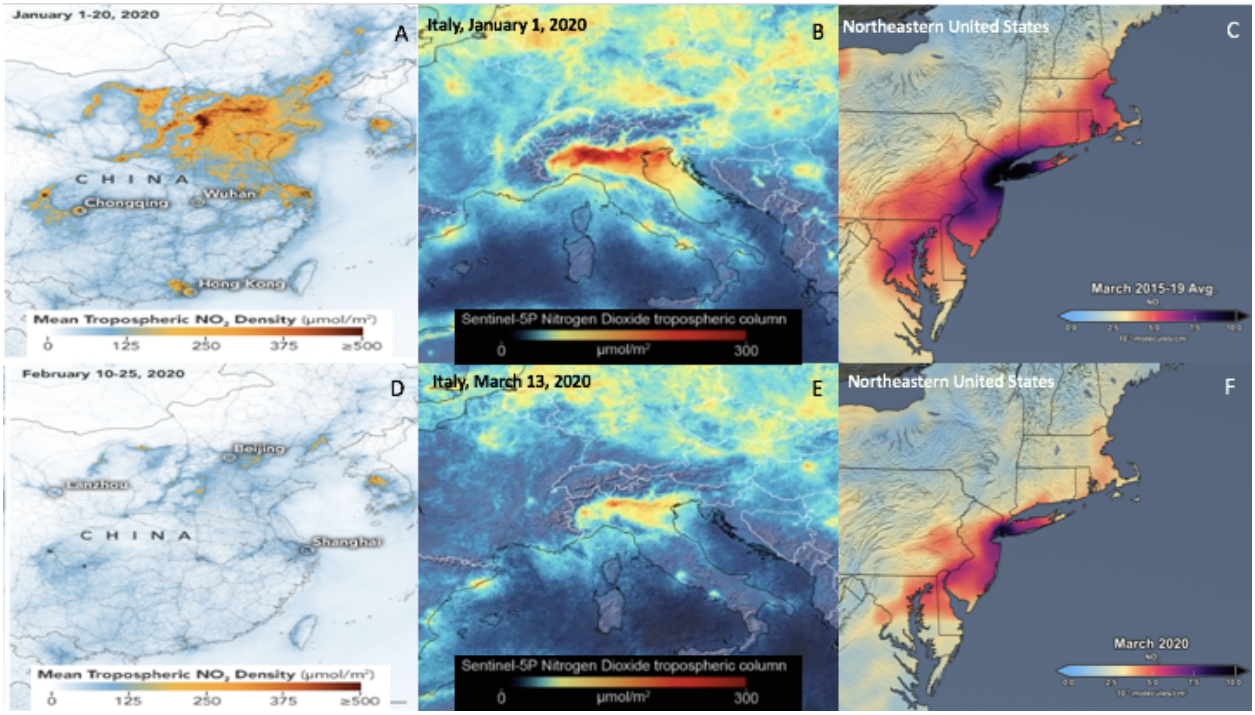

Figure 5. Vertical comparisons of satellite modeling of NO_2 concentrations in Eastern China, Northern Italy, and the Northeastern United States before and during the COVID-19 pandemic. (A) China January 1-20, 2020 average (B) Northern Italy January 1, 2020 (C) Northeastern United States March 2015-2019 average (D) China January 10-25, 2020 average (E) Northern Italy March 13, 2020 (F) Northeastern United States March 2020 average Sources: National Aeronautics and Space Administration and European Space Agency.

Reductions in Regulatory Measurement Levels of Air Pollutants in New York City

In New York City (NYC), trends in criteria air pollutant levels measured by regulatory air monitors since the onset of the pandemic appear to mirror the findings reported by NASA and the European Space Agency. The scatter plots displayed in Figure 6 represent differences in daily composite average levels of criteria air pollutants measured by regulatory monitors in NYC since March 1, 2020 compared with average levels for the same dates in the years 2017-2019. Scatter plots resulting from this calculation were fitted with quadratic polynomial trend lines to clearly delineate temporal trends before and after NYC

began to shut down on March 13, 2020.[115] Data used for this analysis were queried from the New York State Department of Environmental Conservation website and were confirmed to have near identical fidelity to validated data reported to the Environmental Protection Agency.[116,117]

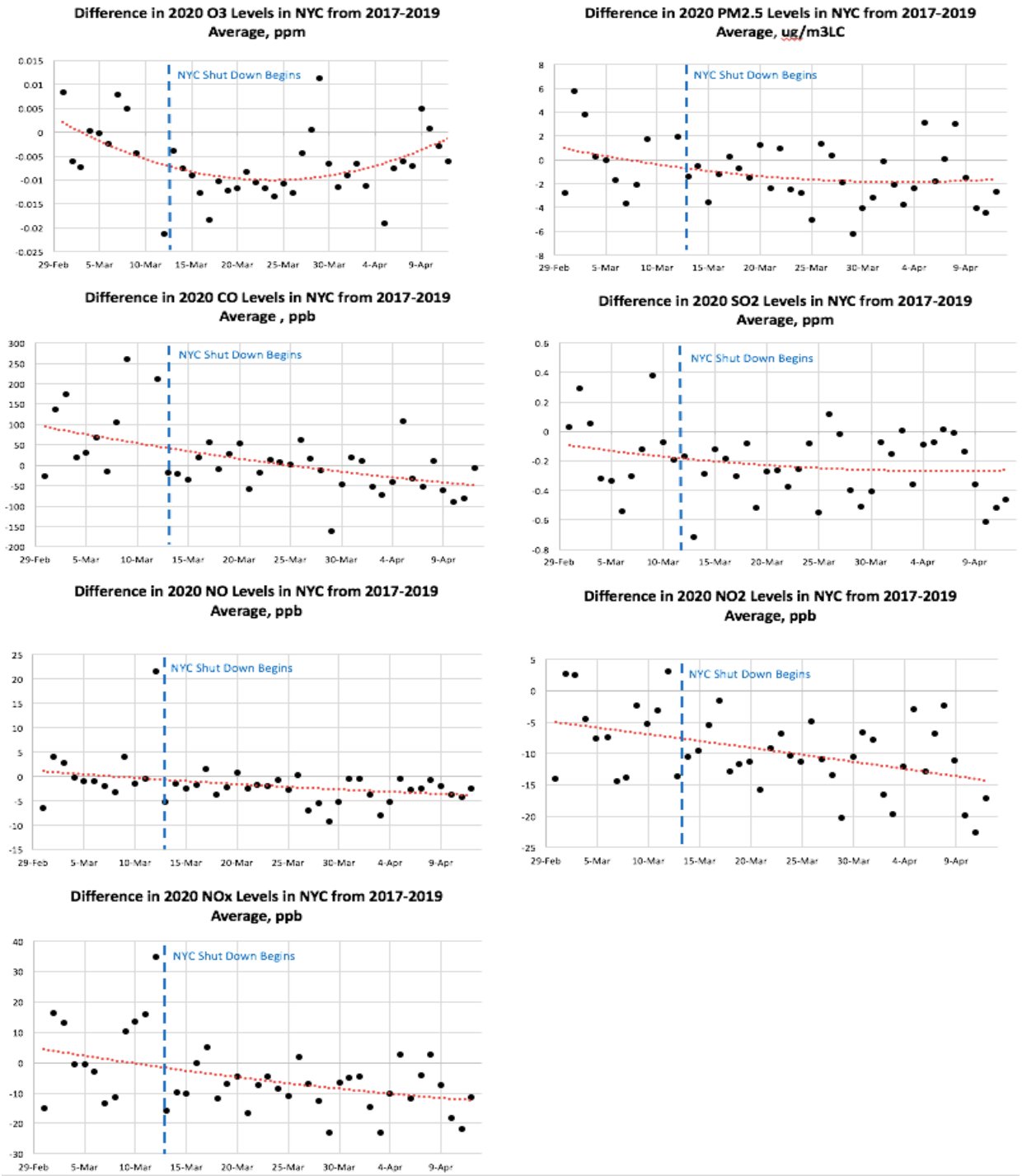

Figure 6. Differences in 2020 composite average of measured pollutant levels in NYC from 2017-2019 averages, March 1 – April 12, 2020.

These plots demonstrate increasing reductions in nearly all pollutant levels measured by regulatory air monitors compared to 2017-2019 averaged levels in the weeks following the shut down in NYC. The exception to this trend is the increase in ozone levels, which is to be expected given the inverse relationship of ozone with dropping carbon monoxide and NO_2 levels. The sharpest reduction was measured for NO_2 followed by NO_x, which supports the estimates produced using satellite data by NASA and the European Space Agency.

Chronic Air Pollution Exposure and Outcomes from COVID-19 Infection

Data from Italy indicate that lethality from COVID-19 infection in areas in the North of the country, specifically the Lombardy and Emilia Romagna regions, is increased compared with other European countries and other regions in Italy. According to data derived from regulatory monitors for multiple criteria air pollutants, these regions are the most polluted in Italy and among the most polluted in Europe. They have also reported a COVID-19 case fatality rate of 12%, compared with 4.5% in the rest of the country. However no adjustment for confounders or effect modifiers such as population age, poverty levels, or quality of local health care systems was completed prior to the reporting of this data.[119]

Another study awaiting peer review specifically analyzed the relationship between chronic $PM_{2.5}$ exposure and COVID-19-related mortality in the United States, excluding New York State. This study did control for a number of confounders and effect modifiers, including race, population density, and several chronic medical conditions. Results estimate an association between chronic $PM_{2.5}$ exposure and COVID-19-related mortality approximately 20 times stronger than the relationship between $PM_{2.5}$ and all-cause mortality.[120]

In NYC, available data do not currently support the specific association of chronic $PM_{2.5}$ exposure and severity of COVID-19 infection. Overall, documented COVID-19 cases in NYC tend to be more severe in nature because testing mostly occurs in tertiary care facilities. Therefore, although mortality rates stratified by zip code are not yet publicly available, on average, reported cases by zip code represent geospatial distribution of relatively severe disease.[121] Although no causal association can be derived from this comparison alone, when the distribution of COVID-19 cases by zip code is compared to the most recent published maps of criteria air pollutants in NYC, the greatest amount of overlap is observed with ozone pollution rather than $PM_{2.5}$ or any other criteria pollutant (Figure 6).[122,123]

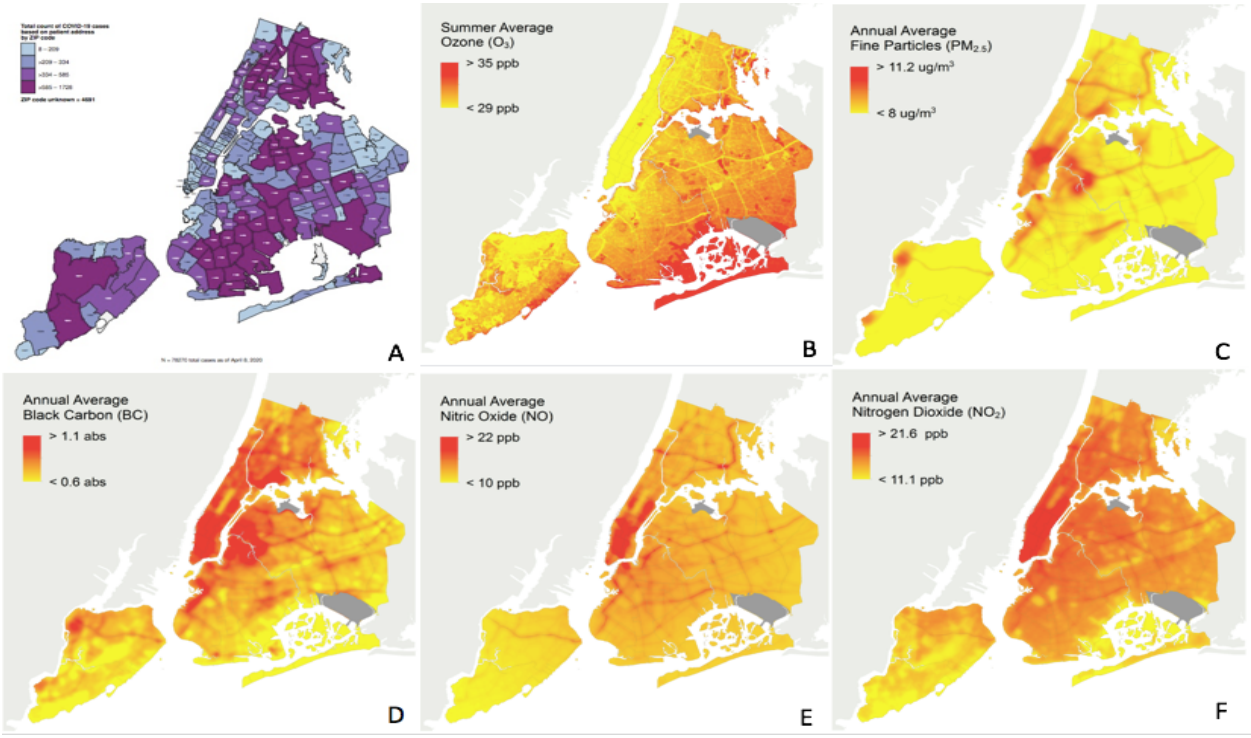

Figure 7. Visual comparison of number of diagnosed COVID-19 cases in NYC by zip code (A) compared with geospatial distribution of criteria air pollutants. (B) Ozone (C) $PM_{2.5}$ (D) Black carbon (E) NO (F) NO_2. Sources: NYC Health COVID-19: Data and New York City Community Air Survey.

In summary, BCP is associated with many known adverse health effects and is now confirmed to accumulate in human tissues beyond the lungs. In this context, mitigation recommendations from global health agencies are increasingly relevant as is the need for more a more equitable distribution of resources for surveillance. The recent COVID-19 pandemic has highlighted the capacity for dramatic reductions in air pollutants over a very short time frame and potentially offered additional insight into the direct relationship between air pollutant levels and health outcomes.

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CAPSTONE GOALS ANALYSIS REFLECTION

My goals upon matriculation into the Johns Hopkins School of Public Health included developing skills in computer science, writing, data analysis, research, and leadership. Although the program does present students with difficult curriculum choices, I do feel I was able to meet these goals through my coursework and capstone. This capstone specifically enhanced my understanding of data analysis, spatial mapping, surveillance, and the pathophysiology of air pollution. Overall, the experience was fun and deeply rewarding. I am confident my new foundation of knowledge, and the network of incredible professionals with whom I had the opportunity to work in the process, have prepared me to meaningfully contribute to the environmental health of populations in my future career.

APPENDIX A - BLACK CARBON POLLUTION AND HEALTH: A REVIEW

Black carbon as a component of air pollution has elicited strong and sustained interest from the public health and scientific communities. It is known not only for its consequences for human health and its warming effect on the climate, but also for the complexities associated with accurately studying its distribution and effects. Black carbon pollution (BCP) is generated primarily as a product of combustion. Levels in the air are measured as an indirect indicator of combustion- and traffic-related particulate pollution and are geographically correlated with human activity and airline travel. Worldwide, the primary sources of BCP are combustion engines, residential burning of wood and coal, oil and coal power stations, burning of agricultural wastes, and forest and vegetation fires.[1,2]

After formation, BCP particles increase in size and in chemical complexity. For example, diesel carbon particles generally range from 1-5 nm immediately after combustion, then coagulate to form aggregate particles ranging from 10-100 nm by the time they exit the vehicle. In the atmosphere, particles further increase in size as they condense with various constituents, including the co-pollutants with which they were emitted, inorganic salts, and water vapor.[3] Solid fuels like wood and coal burn less completely and thus tend to produce larger primary BCP particles (ranging from 50-600 nm), but coagulate and condense over time in a manner similar to diesel fuel.[4]

When measured in the atmosphere, BCP particles are always associated other combustion or atmospheric species. They are universal carriers of chemicals of varying toxicities. BCP particles can be carriers of metals and metalloids such as nickel, vanadium, or arsenic. They may also associate with organic compounds, including polyaromatic hydrocarbons, dicarboxylic acids, quinones, bacterial endotoxin, or a variety of inorganic constituents capable of altering their biologic effects.[5,6]

Toxicokinetics of Black Carbon Pollution Particles

The current scientific consensus supports that BCP particle toxicity is predicated on the size of the particle. Particles recovered from human lung tissue at autopsy are almost exclusively less than 2.5 μm in greatest dimension. Only a small fraction of these are ultrafine particles (particles with a less than 100 nm in greatest dimension), suggesting particles greater than 2.5 μm in greatest dimension become trapped in proximal airways, while ultrafine particles translocate through the alveoli to the bloodstream.[7] Indeed, in human test subjects, after radiolabeled ultrafine carbon particles are inhaled, radioactivity

can be detected in the blood and confirmed to distribute to extrapulmonary organs, but these findings have been difficult to replicate due to lack of specificity of the radiolabeling technique.[8-10] A similar study utilizing gold particles supports the translocation theory, and suggests that smaller nanoparticles (5 nm in greatest dimension) translocate more readily than ultrafine particles with a greatest dimension of 30 nm.[11]

BCP nanoparticles that remain in the lung can form chain-aggregates comprised of carbon particles and other pollutants. They may also accumulate in airway macrophages. The degree of both aggregation and airway macrophage accumulation have been correlated with the amount of BCP in the environment.[12,13] In vitro studies also indicate BCP nanoparticles rapidly aggregate in non-phagocytic bronchial epithelial cells and pulmonary fibroblasts.[14]

In rats, before reaching the tracheobronchial tree, ultrafine BCP particles have been confirmed to accumulate in the nasal mucosa, from where they translocate along the olfactory nerve to circumvent the blood-brain barrier and enter the olfactory bulb of the brain.[15] Thus, the two primary mechanisms by which scientists have observed particle accumulation in extrapulmonary organs is the translocation of ultrafine particles from the alveoli to the blood and from the olfactory nerve to the brain.

Adverse Health Consequences of Black Carbon Pollution

Although the pathogenic mechanisms of action of BCP particles are not completely understood, there is extensive epidemiologic evidence that BCP is independently associated with many adverse health outcomes reflecting disruptions of several physiologic systems within the human body. The evidence appears to be most robust for the

association of BCP with all-cause mortality, and adverse pulmonary and cardiovascular outcomes. There are also associations with adverse neurocognitive, epigenetic, genetic, and perinatal outcomes. In fact, a number of studies have concluded that BCP is the most toxic component of airborne pollution, although this conclusion is not always supported by systematic reviews or meta-analyses.[5,16-19]

The remainder of this review describes the pathophysiology and known associated adverse health effects of BCP. It also summarizes what is known of BCP particle accumulation in the human body. Referenced literature is specific to black carbon particles and excludes studies referencing broader categories of mixed pollutants of which black carbon is a component, such as particulate matter, diesel exhaust, or woodsmoke. To present a more accurate description of the risks of black carbon particles to the general population, studies based on occupational exposures were also excluded.

Mortality from Black Carbon Pollution

Both long- and short-term exposure to BCP is independently associated with all-cause mortality, and mortality from cardiovascular and respiratory causes.[16,20] In the United States, 14,000 deaths are estimated to result from environmental BCP levels on an annual basis in addition to hundreds of thousands of illness cases.[21]

Pulmonary Complications of Black Carbon Pollution

BCP is specifically associated with mortality from and hospitalizations due to respiratory illnesses.[16,20,22,23] It has also been consistently associated with a number of chronic pulmonary conditions, including suboptimal lung development in children, obstructive airway disease in both children and adults, reduced lung function in individuals without

known chronic lung disease, reduced protective effects of exercise on lung function, and increased pulmonary decline in aging adults.

Pathogenic mechanisms associated with black carbon in the lung have been identified. Carbon in the environment is strongly associated with inflammation and oxidative stress in bronchial epithelial cells and airway monocytes regardless of asthma status.[24-29] Moreover, levels of airway inflammation have been in observed to increase or decrease according to short-term changes in BCP in the environment.[30,31] Pro-inflammatory gene demethylation, as observed in atopic children in response to BCP pollution, may partially explain this association.[32] Inflammation and oxidative stress in turn may lead to chronic inflammatory states or autophagy of lung parenchyma.[33,34]

Aside from associated inflammatory and oxidative processes, pulmonary macrophages loaded with BCP particles exhibit subsequent impairment in phagocytosis of pathogens.[35] There is also evidence of systemic inflammation and oxidative stress in individuals with and without pre-existing pulmonary disease after inhalation of BCP that may contribute to pulmonary symptoms.[29,36-38]

Consequences of Black Carbon Pollution for Pulmonary Development

Regardless of asthma status, increased carbon load in airway macrophages due to environmental exposure is associated with decreased pulmonary function in children as determined by spirometry testing. Specifically, carbon load exhibits a dose-responsive reduction in forced expiratory volume in one second, forced expiratory flow between 25 and 75 percent of the forced vital capacity, and forced vital capacity in asthmatic and non-asthmatic children.[39]

Consequences of Black Carbon Pollution for Obstructive Airway Disease

BCP exposure is associated with worse outcomes for individuals with asthma and chronic obstructive pulmonary disease (COPD). Increases in asthma prevalence and severity in both children and adults have been associated with BCP exposure. Specifically, outpatient and inpatient visits for asthma increase for both children and adults when BCP increases in the environment.[40,41] Results are similar when the outcomes of ED visits specifically for allergic rhinitis and allergic asthma are correlated with BCP levels.[42] In adults with COPD, indoor BCP is also associated with decreased pulmonary function prior to bronchodilator therapy.[43]

Association of Black Carbon Pollution with Reduced Lung Function

Black carbon is associated with reduced lung function in adults, reduced exercise-induced improvement in lung function, and increased age-related decline in pulmonary function, even in individuals without known pulmonary disease. As an example, one study specifically demonstrated BCP levels are independently associated with decreased overall lung function in urban women regardless of smoking status, previous asthma diagnosis, or socioeconomic status.[44] Spirometry measures of lung function show less improvement after exercise in healthy adults as concentrations of BCP increase.[45] A similar study showed that BCP offsets the protective relationship between physical activity and airway inflammation in children as measured by fractional exhaled nitric oxide.[46] Long-term BCP exposure is also associated with an increased rate of decline in key measurements of lung function in elderly individuals, even at levels adherent to the Environmental Protection Agency National Air Quality Standards.[47]

Cardiovascular Complications of Black Carbon Pollution

Aside from the aforementioned associated mortality rate from cardiovascular causes, BCP is also independently associated with hospitalizations in adult populations for cardiovascular causes.[23,48] Cardiac conditions for which there is specific evidence for an association with BCP include ischemic heart disease, autonomic dysfunction, arrhythmia, and hypertension.

Association of Black Carbon Pollution with Ischemic Heart Disease

Elevated levels of BCP are independently associated with hospitalizations for ischemic heart disease.[48] Although the exact mechanism of this association has not been described, a number of physiologic pathways have been shown to be disrupted in the presence of black carbon. First, anatomic studies indicate that long-term environmental BCP particle concentration is directly associated with carotid intimal media thickness and plaque formation.[49] Translocated nanoparticles have also been shown to accumulate in the plaque of arteries and at sites of vascular inflammation.[11]

Studies have also shown derangements of inflammation, endothelial function, and platelet activation associated with black carbon particle exposure. For instance, a number of markers of systemic inflammation are upregulated in the presence of black carbon in individuals with risk factors for cardiovascular events such as diabetes or pre-existing coronary heart disease.[50] Prolonged exposure to black carbon is also associated with hypomethylation and increases in markers of endothelial inflammation and dysfunction.[51,52]

In vitro studies indicate black carbon particles may also be internalized by platelets and are able to directly stimulate platelet aggregation and thrombosis by activating the pathways that lead to integrin activation and fibrinogen binding.[53,54] At lower concentrations, particles can also synergize with physiologic agonists like thromboxane A2 and adenosine diphosphate to trigger a platelet response.[54]

Association of Black Carbon Pollution with Arrhythmia

BCP has been associated with reduced heart rate variability in a number of studies, although a dose-response relationship is not consistently apparent.[55,56] It is also associated with increased ventricular ectopy in the elderly.[57] The mechanism underlying these associations does not appear to be clearly described in the literature.

Association of Black Carbon Pollution with Hypertension

Several studies have demonstrated positive associations between both short- and long-term exposure to environmental BCP and both systolic and diastolic blood pressure measurements.[58,59] Short-term increases in black carbon exposure are associated with dose-dependent increases in arterial stiffness measurable by carotid artery ultrasound.[60] The increase in blood pressure may also partially explain the observed associations between BCP and cardiovascular disease and mortality.

Neurocognitive Complications of Black Carbon Pollution

A link has been established between BCP and adverse neurocognitive outcomes in both children and adults. Elevated ambient BCP levels during development are independently associated with higher rates of commission errors and slower reaction times on cognitive

tests in urban children.[61] They were also independently associated with reduced vocabulary, composite intelligence quotients, and memory in a separate study of urban children.[62] Long-term black carbon exposure is also associated with age-related cognitive impairment as measured by the Mini Mental Status Exam. The association is more pronounced in older men with longer blood telomere lengths and higher c-reactive protein levels, suggesting these measurements may be used to predict the impact of BCP on cognitive changes.[63]

Epigenetic and Genetic Changes Associated with Black Carbon Pollution

Epigenetic changes associated with BCP are markers of biologic aging and increased risk of carcinogenesis. Long-term exposure to BCP is linked with telomere attrition, a biomarker of biological aging.[64] Black carbon, even if washed, also exhibits genotoxic effects in in vitro cell lines.[65] BCP exposure is also directly correlated with increased overall placental mutation rates and epigenetic alterations in key DNA repair and tumor suppressor genes, suggesting a vulnerability of affected newborns to carcinogenesis later in life.[66]

Perinatal Complications of Black Carbon Pollution

Selected perinatal outcomes appear to be correlated with environmental BCP. For instance, prenatal exposure to BCP is independently associated with reduced birth weight, particularly in male neonates.[67] In addition, newborns exposed to elevated BCP in utero are more likely to have an increased systolic blood pressure at birth.[68]

Effect Modifiers for Adverse Health Effects of Black Carbon Pollution

Certain populations appear to be particularly susceptible to the adverse health effects of BCP. Specifically, obesity and certain genetic characteristics predispose affected individuals to worse health outcomes attributable to BCP.

Obesity

Obese individuals are more susceptible to several adverse health outcomes linked with BCP. For example, reduced heart rate variability due to BCP exposure is consistently shown to affect obese individuals more than the general population.[69,70] In addition, ventricular ectopy in the elderly is more likely to occur in obese individuals in the setting of increased BCP exposure.[57] Markers of endothelial dysfunction and inflammation are also more strongly associated to BCP in obese individuals than in non-obese individuals.[52] Lastly, infants exposed to BCP in utero are more likely to have a reduced birth weight if born to obese mothers.[67]

Genetics

Genetic profiles appear to modify the outcomes of arrhythmia, hypertension, cognitive decline, and decline of pulmonary function associated with BCP. For example, elderly individuals with specific glutathione S-transferase variants have a higher odds of ventricular ectopy when exposed to BCP.[57] In addition, genes related to oxidative stress have been observed to modify measured heart rate variability in response to short-term BCP exposure.[38] Similar genetic profiles appear to amplify the effect of long-term BCP exposure on decline in lung function.[71] Lastly, carriers of specific microRNA-processing

single nucleotide polymorphisms appear more susceptible to the hypertensive and negative cognitive effects of BCP.[72,73]

Published Evidence of Black Carbon Accumulation in Human Lungs and Extrapulmonary Organs

Most anatomic studies demonstrating BCP accumulation in the human body have been performed on the lung. One of the earliest such studies demonstrated that areas of trapped parenchymal soot deposits in the lung exhibit emphysematous changes, although the mechanism of these changes could not be described at the time.[74] In the 1970s, another anatomic study concluded that lung samples obtained at autopsy contain soot averaging 1.7g per person, with statistically significant associations with age and cerebrovascular accident being listed as a cause of death.[75]

Despite the extensive body of research characterizing the toxicokinetics of black carbon particles in the upper airways of animal models and confirming its translocation through the lungs of humans, few studies have investigated its distribution to human extrapulmonary organs. As previously mentioned, inhaled carbon nanoparticles have been confirmed to circumvent the blood-brain barrier by entering the brain from the nasal cavity via the olfactory nerve in animal models.[15] A similar study conducted in humans confirmed the presence of magnetite (a magnetic non-carbon iron oxide) nanoparticles in the human brain, but no such study involving black carbon has been published.[76] Recently, carbon particles have been identified within the fetal side of the human placenta utilizing white-light generation under femtosecond pulsed illumination as a technique. In this study, black carbon concentration mirrored the mothers' residential BCP exposure during pregnancy.[77] Researchers have also recently used the same technique to confirm black

carbon in urine samples submitted by children, with concentrations also reflecting medium-term to chronic environmental exposure to BCP.[78] It follows then that BCP does circulate in the human body, but its distribution to extrapulmonary organs has yet to be described.