



COVID-19 Immunopathology, Particle Pollution, and Iron Balance

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Authors' contributions

This work was a joint effort between both authors that is part of an ongoing collaboration aimed at providing scientific, medical, public health implications and evidence related to COVID-19, iron balance, and particulate pollution, especially, aerosolized coal fly ash including its use in the near-daily, near-global covert geoengineering activity. Author MW was primarily responsible for medical and public health considerations. Author JMH was primary responsible for mineralogical and geophysical considerations. Both authors read and approved the final manuscript.

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ABSTRACT

The coronavirus (COVID-19) pandemic exploded into a world already reeling from climate change, degradation of natural systems, and pandemics of air pollution and noncommunicable diseases. These pandemics are interrelated; air pollution, the world's biggest killer, is a major contributor to noncommunicable disease. Air pollution is a probable cofactor in the spread and severity of COVID-19. There are shared mechanisms of injury by the emerging COVID-19 immunopathology, ultrafine air pollutants, and chronic degenerative disease. A key feature of each is oxidative stress, including that caused by iron dysregulation. Exogenous combustion-derived magnetite nanoparticles found in human brains and hearts are strongly implicated in the development of

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cardiometabolic and neurogenerative disease. Altered iron balance favoring excess reactive or misplaced iron is probably the most important predisposing condition for severe COVID-19 infection. Ultrafine-particle/nanoparticle toxicity and COVID-19 immunopathology on the subcellular level are both characterized by iron dysregulation, mitochondrial dysfunction, and endoplasmic reticulum stress. Primary sources of the most damaging ultrafine pollution particles are fossil fuel combustion, vehicle emissions, and coal fly ash utilized in undisclosed tropospheric aerosol geoengineering. The same ultrafine particles when emitted or placed into the troposphere alter the world's cloud layers and reduce atmospheric convection, directly contributing to climate change and global warming. Pandemics can only be tackled by international cooperation. Immediate steps that must be taken include monitoring and control of ultrafine particulate air pollution, and prompt cessation of geoengineering operations.

Keywords: *Virology; pandemic; cardiology; hematology; aerosols; coal fly ash; particulate air pollution; magnetite; nanoparticles; geoengineering.*

1. INTRODUCTION

Since its 2019 emergence in China, the coronavirus SARS-CoV-2, also known as COVID-19, has wrought illness, suffering, death, financial disaster, and much human misery. Like the unprovoked attack on Pearl Harbor, December 7, 1941, [1] its consequence was to awaken a sleeping giant, not only in America, but throughout the world.

Understanding in a more fundamental way how the virus attacks and alters the human body, one of the moral imperatives awakened by the COVID-19 Pandemic, is one purpose of this Review.

The former Director-General of the World Health Organization recently pointed out that the simple act of breathing is killing seven million people a year and injuring billions more, and stated [2]: *"No one, rich or poor, can escape air pollution. Despite this epidemic of needless, preventable deaths and disability, a smog of complacency pervades the planet."* Some might say *"smog of complacency"* as few individuals have been willing to question policies that not only allow, but greatly augment air pollution. That may change now.

Another of the moral imperatives awakened by the COVID-19 Pandemic is to understand in a more fundamental way the spectrum of bodily harm caused by pollution, and especially, its role in spreading the virus, and exacerbating the severity of its attack on human populations.

This review explores the emerging immunopathology of COVID-19 and shows how the pandemics of air pollution, noncommunicable disease (NCD) and COVID-19 are interrelated.

Air pollution, the world's greatest killer, is a major cause of noncommunicable diseases (NCD's). Age and chronic disease (NCD's) predispose to more severe COVID-19 disease. Air pollution, COVID-19, and many NCD's share common features of iron dysregulation, inflammation, and subcellular organelle toxicity. The universal exposure to combustion-derived UFP's and nanoparticles in human cells and tissue produces very similar pathological features. The ultrafine fraction of air pollution in the troposphere is related to climate change and global warming.

2. THE PANDEMIC

The COVID-19 pandemic has become the most important infectious disease problem of the century and one of the greatest challenges to ever face mankind. The novel coronavirus, SARS-CoV-2, which emerged in China in 2019, was found to be responsible for the disease. SARS-CoV-2, now known as COVID-19, has rapidly circled the globe and affected every continent except Antarctica. COVID-19 follows outbreaks of two other deadly Beta-coronaviruses, severe acute respiratory virus syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012 [3]. COVID-19 is likely to cause immense human suffering and death in a world already racked by climate change and rapid global warming, pollution, ozone layer depletion, and the decimation of ecosystems and wildlife. Ecosystem degradation from anthropogenic activities has greatly accelerated outbreaks of emerging and zoonotic infectious diseases in the past century, The COVID-19 pandemic should be considered an indirect consequence of these environmental changes [4].

3. COVID-19 AND ITS EMERGING IMMUNOPATHOLOGY

The pandemic poses vast health, economic, environmental, and social challenges to the human population [5]. The COVID-19 pandemic is bound to have a devastating effect on the world's economy, in part because of pre-existing global wealth disparity, imposed austerity, and deterioration of public health. Although the future severity of the pandemic is difficult to predict and quantify, there will almost certainly be a vicious downward spiral of illness and impoverishment. Global cooperative efforts based on sound scientific and public health principles will be necessary to bring the COVID-19 pandemic under control [6].

Coronaviruses are enveloped, positive stranded RNA viruses which infect both man and animals. The majority of known human coronaviruses cause mild respiratory disease. SARS, MERS, and COVID-19 belong to the group of beta coronaviruses that can cause severe lower respiratory infection and sometimes fatal severe respiratory syndrome [7]. COVID-19 is highly transmissible person-to-person, by virus-containing droplets, secretions, and aerosolized particles [8].

Coronaviruses bind to receptors to enter and infect cells. COVID-19 uses its spike protein to bind to the peptidase angiotensin-converting enzyme 2, or ACE2. The interaction between COVID-19 and ACE2 in part determines tissue tropism and progression from mild to severe disease. ACE2 is highest in nasal epithelial cells with lesser amounts in lung epithelial cells, consistent with disease pathology. Breakdown of the lung epithelial-endothelial barrier in susceptible persons might trigger viral dissemination and widespread or systemic disease. The strategies of most of the vaccine candidates, convalescent plasma, and monoclonal antibodies are aimed at preventing the binding of COVID-19 spike protein to the ACE2 receptor [9].

The body's defense against coronavirus includes not only cellular and humoral (i.e. antibody) immunity, but also the production of proinflammatory cytokines. Effector cytokines like interferon reduce viral replication and promote antigen recognition, thereby contributing to viral containment. However, SARS-CoV-2 has the potential to sabotage the host's immune

response. Infection of certain immune cells by the virus can inhibit or counteract interferon [10]. Impaired clearance of virus due to both host and pathogen factors can lead to an "over-reaction" of the immune system characterized by cellular infiltration and apoptosis (programmed cell death), and a proliferation of inflammatory mediators released by effector cells.

Severe COVID-19 disease is characterized by "cytokine storm" and macrophage activation syndrome [11]. An excessive inflammatory response is thought to be a major cause of disease severity and death in patients with COVID-19 infection, and is associated with high levels of circulating cytokines, profound lymphopenia (lymphocyte depletion), and mononuclear white blood cell infiltration into the lungs, heart, spleen, lymph nodes and kidney [12]. Findings in critical ill patients with COVID-19, including fever/confusion, high ferritin, LDH, IL-6, C-reactive protein, and coagulation abnormalities, suggest cytokine storm syndrome [13].

While most healthy persons survive the initial phase of COVID-19 replication and associated inflammation, a small percentage of individuals have a secondary inflammatory response to the virus after they have already developed IgG antibodies to the virus [14]. This delayed response is likely due to antibody dependent enhancement (ADE), which occurs with other viruses including dengue and influenza [15, 16]. Early and/or non-neutralizing antibodies bind to virus and the resulting virus-containing immune complexes are taken up by Fc receptors on monocytes and macrophages. This kind of viral uptake can result in persistent viral replication in immune cells and virus-antibody (that is, immune complex)-mediated inflammation and tissue damage [17]. Blood vessel occlusion and infarction during COVID-19 infection show features of immune complex vasculitis [18], and the COVID multisystem poly-inflammatory syndrome (MIS-C) in children resembles Kawasaki, which is most likely an immune complex disease [19]. Both the quality and quantity of antibodies dictate the functional outcomes of ADE [20]. Clinical support for ADE immunopathology comes from the observation that severe SARS/COVID disease often occurs after 2 weeks of illness, when viral loads are declining, but antibodies are rising. Antibody-dependent SARS coronavirus enhanced infection is mediated by antibodies against spike protein [21].

The emerging paradigm of COVID-19 immunopathology involving ADE and immune complexes has vast implications for testing strategies, viral persistence, re-infection, vaccine development, and therapeutics. The detection of SARS-CoV-2 by IgM and IgG antibodies along with viral PCR/antigen tests provides the basis for diagnosis. However, early production and higher titers of IgG antibody are often associated with more severe COVID-19 disease, consistent with ADE [22]. Experience with SARS and MERS show that some antibodies directed against the spike protein of the virus can facilitate uptake by Fc receptors on human monocyte and macrophages; these cells do not normally express ACE2 receptors. For both viruses, this process is dependent on antibody concentration.

Vaccines against SARS and MERS in animal studies have not been effective, with a number of these vaccines triggering immunopathology and severe lung disease upon challenge with the virus. Monoclonal antibodies and convalescent serum must be carefully tested for ADE effects [23]. It has been shown that highly diluted antisera against SARS-CoV-2 enhances SARS-CoV infectivity [24]. COVID-19 not only induces immune responses but produces uncontrolled inflammation and cytokine release in severe disease. There is a strong association between SARS-CoV-2 induced immunopathology and poor survival of patients. Antivirals, steroids, and immunoglobulin treatment have limited efficacy in persons with severe COVID-19 disease. However, targeting the specific COVID-19 immune profiles, such as by enhancing innate immunity or inhibiting inflammation, can be useful treatment strategies for more severe cases [25]. It is becoming evident that COVID-19 can lead to significant morbidity and residual effects in many "recovered" patients. In this regard, a hallmark of immune complex disease is viral persistence [26].

4. CENTRAL ROLE OF IRON IN HEALTH AND ILLNESS

Iron is crucial to basic biological functions including DNA/RNA synthesis, mitochondrial function, and production of ATP. Viruses depend on intracellular iron in order to replicate. Both host and pathogen require iron in the evolutionary process, so the innate immune response must control iron metabolism to limit its availability during infection [27].

Systemic iron homeostasis is controlled by the hepcidin-ferroportin axis and cellular iron uptake

is mediated by interactions between iron-bound transferrin and transferrin receptors on cells. The transferrin receptor (TfR) is a common portal for many viruses to enter cells, although not yet studied in the case of COVID-19 [27, 28]. Iron metabolism is tightly regulated by iron absorption in the gut, iron storage in the liver and spleen, iron transport in blood, iron utilization (primarily in bone marrow for erythropoiesis), and iron recycling by macrophages [29]. Tissue resident macrophages regulate local iron availability and modulate the tissue microenvironment, supporting proper cellular and tissue function [30].

Increasing evidence suggests that inflammation, oxidative stress, and altered iron homeostasis are linked at the systemic level. Ferritin is the main iron-storage protein in the body. Iron in ferritin is normally bound and released in a controlled manner. During infection, increases in ferritin may deprive pathogens of iron and protect immune function. Conversely, ferritin may be a key regulator of immune dysregulation, especially in situations of extremely high levels of ferritin (hyperferritinemia) via direct immune suppression and pro-inflammatory effects. Certain conditions of hyperferritinemia (with disruption of ferritin and reactive iron release) identify patients at high risk of severe disease or even death while its resolution predicts recovery [31]. Shifting of immunoregulatory balances caused by iron excess can lead to deleterious physiological effects. Disease states characterized by high body stores of iron increase virus replication and complicate clinical management [32].

5. IRON DYSREGULATION AND COVID-19

Although COVID-19 has been considered an infectious/inflammatory disease primarily affecting the lungs, there is growing recognition that this virus can affect multiple organ systems by using different pathways of injury. Uptake of the virus into monocytes and macrophages by Fc receptors with subsequent dissemination throughout the body is one such pathway.

Hemoglobinopathy with associated hypoxemia and iron dysregulation appears to be a feature of more severe disease with COVID-19 [33]. During the cytokine storm produced by COVID-19, high levels of IL-6 are produced, which stimulates ferritin and the synthesis of hepcidin. Hepcidin sequesters iron in macrophages, leading to

increased intracellular ferritin and reduced iron efflux from cells. Excess intracellular iron creates reactive oxygen species and impairs mitochondrial function. Damage to the cell can result in ferroptosis, a type of programmed cell death caused by iron excess [34].

When ferritin is released from damaged cells, it loses part of its inner iron content giving rise to high levels of “free” or reactive iron. Free iron worsens inflammation by the production of reactive oxygen species (ROS's) and can induce a marked pro-coagulant effect. Oxidative stress on red blood cells produced by reactive iron predisposes to dense clots that can produce stroke [35]. Iron laden macrophages are observed in tissue (e.g. bone marrow) of persons who died from severe COVID-19 disease. In humans with HIV immunodeficiency and/or hepatitis C virus infection, iron overload is associated with more pronounced disease, with evidence that the virus itself may enhance macrophage iron loading [36]. Iron disrupts the balance between M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophage phenotype populations [37].

During the past century, research has shown that excessive or misplaced iron in specific tissues, cells, and subcellular sites can produce a wide array of acute and chronic diseases. Iron excess is recognized as a risk factor for infection, neoplasm, metabolic disease, cardiopulmonary disease, and neurodegenerative disease [38]. The most important co-morbidities associated with severe COVID-19 infection include metabolic disease, e.g. obesity and diabetes, cardiovascular disease (including hypertension), respiratory disease (including COPD and asthma), cancer, and chronic liver and kidney disease [39]. Altered iron homeostasis is a common risk factor linking many of these co-morbidities to increased morbidity and mortality from COVID-19 infection.

Epidemiological evidence strongly supports the association of iron dysregulation with diabetes and heart disease [40]. Iron imbalance affects chronic metabolic diseases, glucose and lipid metabolism, fatty liver disease, and obesity. Iron excess increases lipid peroxidation that in turn modifies the fatty acid profile of cell membranes, leads to damage of cellular organelles, and impairs mitochondrial function [41]. Increased serum ferritin predicts the development of hypertension in men [42], and arterial stiffness is associated with increased ferritin and deposition

of iron in vessels walls [43]. The high rate of cardiomyopathy in persons with hemosiderosis and transfusion iron overload suggests that iron build-up in the heart has an important role in the development of heart failure [44].

Obesity is a major risk factor for COVID-19. Increased dietary availability of iron through fortification of processed food is a factor related to the global epidemic of obesity [45]. Iron dysregulation is common in obesity [46], chronic liver disease [47], chronic kidney disease [48], and many cancers [49]. Heavy alcohol usage and smoking cigarettes can worsen iron excess in the body [50].

In summary, altered iron balance favoring excess reactive or catalytic iron may be the single most important underlying pathological process predisposing to severe COVID-19 infection and associated inflammation and immunopathology.

6. AIR POLLUTION – THE WORLD'S LEADING KILLER

The modern plague of air pollution is the greatest killer of our age. Air pollution is the leading environmental cause of disease (morbidity) and death (mortality) in the world. [51, 52]. Air pollution particulates penetrate deeply into the lungs and systemic circulation; contributing to stroke and neurodegenerative disease [53, 54] heart disease [55-57], lung cancer [56, 57], COPD [58, 59], and respiratory infections [60].

Air pollution is thus one of the main contributors to yet another global pandemic; that of noncommunicable diseases. Air pollution causes both acute and chronic disease, potentially affecting every organ system in the body. Tissue damage can result directly from toxic particles that gain access to organ systems, or indirectly by systemic inflammation. Oxidative stress caused by air pollution activates pro-inflammatory signaling which sets off a cascade of events that impact distant organ systems. Oxidative stress in cells and tissues is a central mechanism by which PM exposure leads to injury, disease, and mortality. The damage from particle pollution is cumulative over time [61].

Ambient air pollution is a leading cause of excess mortality and loss of life expectancy (LLE), especially caused by cardiovascular disease. Globally, the loss of life and life expectancy from air pollution exceeds, by a large margin, that of infectious disease and many other causes.

Although air pollution affects everyone, it causes more severe disease in those with the most exposure and greater susceptibility. The fraction of preventable loss of life expectancy (LLE) from anthropogenic air pollution attributable to fossil fuels is nearly two-thirds (2/3) globally, and up to 80% in high-income nations [62].

7. HORRORS OF TROPOSPHERIC AEROSOL GEOENGINEERING

A deliberate form of air pollution and existential threat to the biosphere is posed by tropospheric aerosol geoengineering. For decades, several countries and entities including the U.S. military have been co-opted into the aerial spraying or injecting particulates into areas where clouds form for purposes of weather modification, climate intervention, communication systems, weather warfare or defense, etc. [63]. There is no truthful public disclosure concerning these operations, despite the obvious particulate trails observed overhead.

Disinformation claiming that the particulate trails represent harmless ice-crystal “contrails” stands in conflict with direct observation, and is disputed by scientific evidence [64]. Aircraft contrails form only briefly in cold, humid atmospheric conditions, unlike the particulate trails that spread out into cirrus-type clouds or even a white haze [65]. Particulate pollution emplaced into the troposphere traps heat that would otherwise be removed by convection [66]. These aerosols alter natural weather patterns, often creating either “drought or deluge” [67], poison the environment [68], damage the protective ozone layer [69], cause global warming [66, 70], and are toxic to nearly all biota [71-74].

Several independent lines of evidence point to coal fly ash as the main particulate that is being sprayed into the atmosphere to alter Earth's natural environment [75]. When coal is burned, the heavy ash settles, while the light ash, coal fly ash (CFA), forms above the burner and would exit the smokestack if not electrostatically trapped and collected as is required in Western nations. Readily available throughout the world, CFA is inexpensive and requires little processing before being deployed in aerosolized form in the atmosphere. Primary components of CFA include aluminum silicates and an iron-bearing fraction which includes magnetite (Fe_3O_4). CFA contains numerous toxic trace elements, unconsumed carbon, and even radionuclides.

Concentrations of these trace elements in CFA are typically higher than those found in the Earth's crust, soil, or even solid coal [76]. CFA makes atmospheric water more electrically conductive because of the many dissolved, ionized elements [63].

8. ROLE OF AIR POLLUTION IN SPREAD AND SEVERITY OF COVID-19

Airborne transmission has been identified as the primary route of spread of COVID-19 on a global basis. Several lines of evidence now point to particulate pollution as a possible co-factor in the COVID-19 pandemic, specifically, as a potential means of viral transport, exacerbating susceptibility and severity of the disease, and altering the immune response to the virus [77]. During the outbreak of severe acute respiratory syndrome (SARS-CoV-1) in 2003, patients from areas with high air pollution indices (API's) showed a 200% increased relative risk of death compared to people from areas with a low API [78]. SARS-CoV-2 RNA has been isolated from particulate matter (PM) in a study conducted in Northern Italy, suggesting that PM in air pollution may act as a vector for transmission of COVID-19 [79].

Coal fly ash with its many fine and ultrafine particles, and notably with hollow cavities [80, 81] (Fig. 1), has been suggested as a possible carrier of respiratory viruses [82]. It has been shown that long-term exposure to the gaseous pollutant NO_2 in air pollution may be one of the most important contributors to fatal COVID-19 infections in many regions of the world [83]. Another study showed that exposure to $\text{PM}_{2.5}$, particulate matter less than $2.5\mu\text{m}$ across, is a significant predictor of the number of new COVID-19 cases and related hospital admissions [84].

A newly published study from Italy showed new cases of COVID-19 are positively related to PM and Air Quality Index, that dry air supports COVID-19 transmission, and that outdoor airborne aerosols are possible routes of COVID-19 diffusion [85]. Air pollutants increase host susceptibility to viral respiratory infections by increasing epithelial cells permeability to viral receptors and reducing host defense, thus impairing macrophage function and phagocytosis, antigen processing, and the expression of natural killer and cytotoxic T-cells. Pollutants may also increase the virulence of COVID-19 [86].

Coal is the most abundant fossil fuel. Because of the rapid growth of coal-fired power plants and industries, the emissions of particulates (coarse, fine, and ultrafine) from these activities are of great concern. There is a direct relationship between human morbidity and mortality and air pollution produced from these kinds of particles [87]. Fine particulate matter derived from combustion sources delivers the most potent and harmful elements of air pollution. The most adverse effects are caused by the combustion-derived ultrafine particles and nanoparticles that contain reactive organic particles and transition metal components [88].

One of the mechanisms for particle-related infections is an accumulation of iron by surface functional groups of PM. Since iron correlates with the presence of surface functional groups, the risk of infection continues while the particle is retained [89]. Coarse particles (10 μm or less, PM_{10}) induce innate immune responses via toll-like receptors, while fine (2.5 μm or less, $\text{PM}_{2.5}$) and ultrafine particles (0.1 μm or less, UFP) induce reactive oxygen species in alveolar macrophages by transition metals and/or polyaromatic hydrocarbons (PAH's) [90].

There are similarities between inflammation caused by particulate matter and inflammation caused by COVID-19. For example, particulate matter induces cytokine expression in human bronchial cells [91], angiotensin II (ACE2) can be a molecular target of particulate matter [92], ambient PM accelerates coagulation via the cytokines like IL-6 [93] and $\text{PM}_{2.5}$ affects macrophage M1 polarization [94]. Abnormal macrophage responses and macrophage

activation syndrome can be induced by SARS-Co-V [12] and air pollution particulates [95].

9. MAGNETITE AND HUMAN DISEASE

Magnetite (Fe_3O_4) is an iron oxide mineral occurring naturally in Earth's surface rocks and sand [96] and industrially-produced in coal fly ash [97]. Biogenic magnetite crystals occur in the bodies of a wide variety of organisms including man. Magnetite likely has several vital life functions, as for example, the detection of magnetic fields [98]. Analysis of human tissue shows the presence of ferromagnetic, fine-grained magnetically interacting particles including the heart, liver, and spleen [99]. Magnetite biomineralization in the human brain was first described in the 1990's [100].

Brain tissue contains biogenic magnetite between 5 and 100 million single-domain crystals per gram. These biogenic ferrimagnetic particles are known to be exquisitely sensitive to external electromagnetic fields via a resonance/vibrational (vs. thermal) mechanism [101]. Human biogenic magnetite nanoparticles tend to be single domain size, high chemical and crystalline purity, arranged in chains or clusters and associated with lipid coatings near the cell membrane [102].

In 2016 Maher et al. [103] showed there were two types of magnetite in brains of persons with cognitive deficits from highly polluted areas: euhedral biogenic particles and spherical exogenous particles most likely arising from air pollution. Fig. 2 presents a morphological comparison of spherical magnetite particles in amyloid cores of Alzheimer's disease, from Plascencia-Villa et al. [104] with spherical coal fly ash magnetic particles from Vu et al. [105].

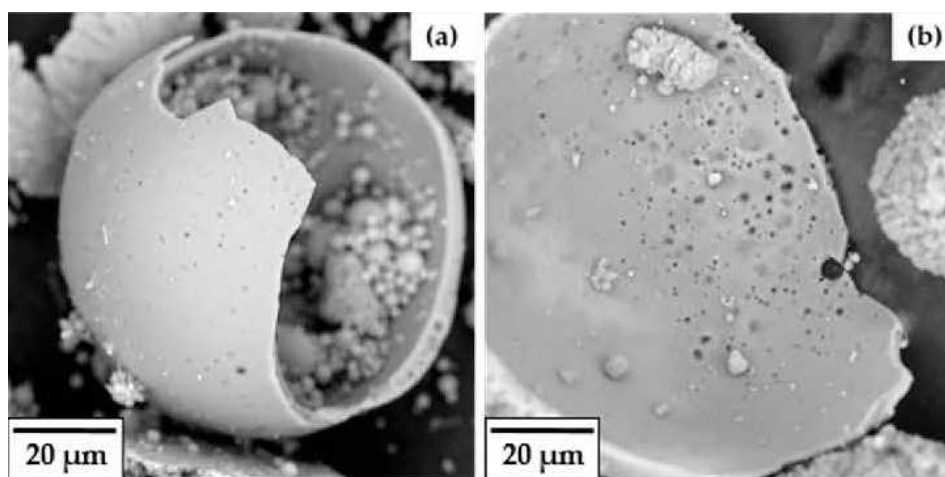


Fig. 1. SEM image of coal fly ash hollow cenosphere. From Yoriya and Tepsri [80]

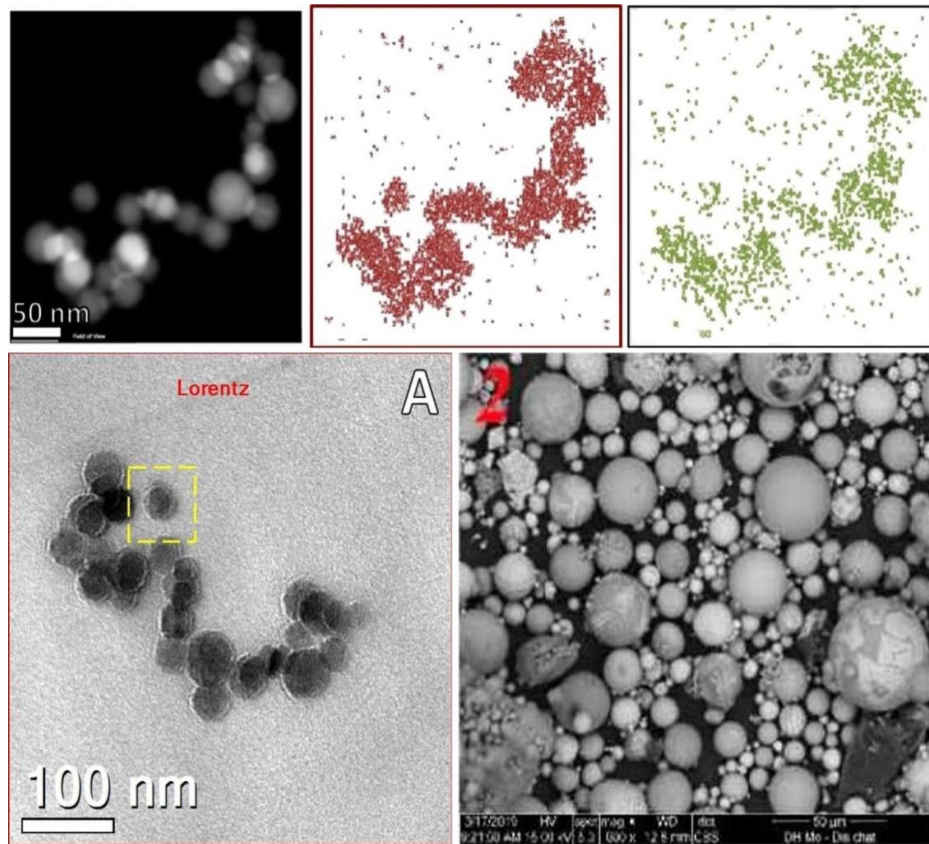


Fig. 2. High-resolution analytical imaging of spherical magnetite particles in amyloid cores of Alzheimer's disease, upper left plus lower left. EDX mapping of iron, upper center, and oxygen, upper right, from [104]. Note morphological similarity with spherical magnetic particles from coal fly ash, lower right, from [105]

More recently, similar combustion and friction-derived magnetic air pollution nanoparticles were found in hearts of persons from highly polluted areas. The organelles and cellular structures associated with these pollution particles showed significant abnormalities.

The health impact of up to 22 billion exogenous magnetic particles per gram of heart tissue is likely to reflect surface charge, ferrimagnetism, redox activity and associated oxidative stress. Exposure to iron-rich combustion-derived nanoparticles, including children and young people, is almost certainly a major risk factor for the development of cardiovascular disease [106]. While biogenic magnetite in tissue serves essential life functions, magnetite in excess from exogenous sources causes harm and disease [107]. The findings of countless combustion-derived magnetic spherical nanoparticles in both human brains and hearts is irrefutable evidence of the near-universal contamination of humanity

by the iron oxide/magnetite fraction of air pollution [108]. Furthermore, these spherical particles precisely match the iron/magnetite nanoparticles in coal fly ash and certain combustion/diesel fumes [108, 109].

Ultrafine particles (UFP's) and nanoparticles, that fraction of particulates less than 0.1 μm , are the most abundant air pollutants from anthropogenic sources. Ultrafine (0.1-1 μm) particles and nanometer-sized particles (< 100 nm) are both found in coal fly ash. Transmission electron microscopy reveals that the ultrafine fraction of CFA is a rich source of magnetite nanoparticles [110].

There are a growing number of reports of pulmonary toxicity from the inhalation of magnetite nanoparticles. Size fractionated magnetite effects on lung epithelial cells include cytotoxicity, genotoxicity, and increased reactive oxygen species [111]. Lung epithelial cells

treated with different concentrations of magnetic iron oxide nanoparticles showed magnetite-treated vs. control cells induced oxidative stress, depleted antioxidant levels, and increased apoptosis [112].

Iron oxide nanoparticles alter macrophage phenotype, iron metabolism, and stimulate migration and invasion [113]. Iron oxide nanoparticles can affect both cellular immunity [114], and humoral (antibody system) immunity [115]. UFP's are the most toxic particles based on their greater surface-to-mass ratio, their larger content of redox active compounds, and their ability to penetrate cell walls [116].

Once deposited deep into the lung, UFP's, unlike larger particles, can gain access to the blood circulation and affect distant organ systems, including both the heart and brain [117]. In addition to penetration of UFP's through lung tissue into circulating cells like red blood cells, these particles can be phagocytized by macrophages and dendritic cells and carried throughout the lymphatic system. The deposition of UFP's into tissue like heart and brain is cumulative over time, gradually increasing oxidative stress [118].

10. TOXICITY OF ULTRAFINE PARTICLES IN HUMAN TISSUE

Translocation of inhaled nanoparticles into systemic circulation and accumulation at sites of vascular inflammation provides a direct mechanism that can explain the link between environmental nanoparticles and cardiovascular disease [119]. Iron is usually the dominant metal species in the solid fraction of UFP's that is produced and emitted by combustion sources.

In heart tissue iron-rich pollution nanoparticles are concentrated in intracellular structures and organelles including endoplasmic reticulum (ER) and mitochondria. Iron-driven mitochondrial dysfunction with increased reactive oxygen species are thought to play an important role in the initiation and progression of cardiovascular disease [120].

In the brain, magnetic combustion-derived nanoparticles are deposited in cells including microglia and neurons and they too are found in and produce abnormalities of mitochondria, endoplasmic reticulum, and mitochondrial-ER contacts (MERC's). These highly oxidative particles are a source of mitochondrial

dysfunction and accumulation of misfolded proteins including tau, B-amyloid, and synuclein, which are early hallmarks of cognitive deficits and dementia [121].

Recently, high resolution scanning/transmission electron microscopy revealed abundant nano-sized aggregates containing carbon and iron rich, ferrimagnetic pollution-derived particles in human placentas. The inhaled, metal-bearing air pollution-derived particulate matter was taken up by macrophage-enriched placental cells. Thus the human placenta and presumably the fetus appear to be a target for these same particles [122].

Endoplasmic reticulum is a crucial organelle involved in proper protein folding. Reactive oxygen species produced in the mitochondria and ER lead to a misfolding of proteins and apoptosis, which likely contributes to various degenerative diseases [123]. A variety of nanoparticles (NP), especially metal based NP's, induce this ER-stress mediated pathway in vitro and in-vivo. These studies suggest that ER stress could be a primary mechanism responsible for NP-induced intracellular toxicity [124].

Note the endoplasmic reticulum-mitochondrial junction is required for iron homeostasis [125]. The coronavirus spike protein induces endoplasmic reticulum stress and triggers innate immune responses [126]. Accumulating evidence indicates that induction of ER stress and unfolded protein response (UPR) constitutes a major component of coronavirus-host interaction [127].

11. AEROSOL PARTICLES – MAJOR EFFECT ON CLIMATE AND PUBLIC HEALTH

Recently, abundant exogenous nanoparticles were found in human serum (healthy subjects) and pleural fluid (from patients with various diseases) [128]. These nanoparticles showed a wide diversity of chemical species, concentration, and morphology. Via chemical multi-fingerprinting (including elemental fingerprints, high-resolution structural fingerprints, and stable iron isotopic fingerprints) of NP's, the sources were found to be abiogenic, and mostly of combustion-derived particulate emission. The nanoparticles included many magnetite nanoparticles highly resembling the pollution particles previously found in heart and lungs.

Amorphous spherical Si, O, and C NP's showed an elemental fingerprint of coal fly ash, while Hg-bearing crystal NP's also suggested this source [128].

Ultrafine particles from coal are rich in Si, Al, Fe, Na, K, Mg, Ca, Ti, Mn, Co, Ni, Zn, V, Cr, Cu, Sb, As, Se, S, and Cl. UFP's from coal combustion are more toxic and reactive to human tissue for the following reasons: (1) Higher concentrations of toxic and volatile compounds are adsorbed in the UFP's than the coarse or fine fractions (with enrichments up to 50-fold), (2) Iron oxides in the UFP fraction are highly reactive and increase oxidative stress, and (3) There is unburned carbon in the UFP's, and carbonaceous content correlates with particle toxicity, possibly related to the oxygenated functional groups on the surface [129].

Most official regulations and air quality standards are focused on PM₁₀ and PM_{2.5} and there are no widely standardized UFP-specific measurements, reporting method, or emission standards. There are limited scientific studies of the human effects of ultrafine particles [130]. Ultrafine particles from smokestacks generate excessive numbers of tiny cloud condensation nuclei, rather than forming large aerosols. Concurrent reduction of cloud droplet size modes by the introduction of excessive UFP's into the atmosphere results in diverse undesirable effects, such as causing either drought or flooding. These particles affect both climate change and the global hydrological cycle, thus affecting public health both directly and indirectly [130-132].

12. ELECTRO-POLLUTION, IRON AND COVID-19

Electro-pollution likely plays a role in the toxicity of exogenous magnetite pollution particles which are deposited in human cells and tissues. Both biogenic and exogenous magnetite pollution particles absorb and transduce a variety of man-made electromagnetic frequencies. Mechanically sensitive ion channels can open or close from the movement of magnetite in response to external electromagnetic fields. This transient opening of membrane pores allows calcium and other ions to enter cells [101].

It is well-known that electromagnetic fields can produce their non-thermal biological effects by activation of voltage-gated calcium channels [133]. Voltage-gated calcium channels are also

an alternative route for iron entry into neuronal cells under conditions that promote cellular iron overload toxicity [134]. In the heart, L-type calcium channels (LTCC) are high capacity pathways of ferrous iron (Fe²⁺) uptake into cardiomyocytes, especially under iron overload conditions [135].

Recently it was shown that radiofrequency (RF) waves activate ferritin-tagged channels via a biochemical pathway. Radiofrequency waves interact with ferritins, increasing the levels of free iron, which produce reactive oxygen species and oxidize membrane lipids [136]. Since cytokine storm and inflammation are both linked to iron dysregulation in severe COVID-19 infection, this immunopathology could be enhanced in the extremely high EMF environment of the hospital intensive care unit.

13. HIGHLIGHTS AND PRINCIPLES

1. COVID-19 is the most important infectious disease of the past century and one of the greatest challenges to ever face mankind.
2. Viral uptake by virus-containing immune complexes by Fc receptors on immune cells is a pathway of immunopathology in COVID-19 infections.
3. There is an emerging paradigm of severe COVID-19 infection as a multi-system, antibody and immune complex-mediated, and possibly persistent viral disease
4. The probability of antibody-dependent enhancement of infection associated with serious COVID infections makes the prospect of a safe and effective vaccine and the ultimate eradication of the virus much less likely.
5. COVID-19, like other viruses, depends on intracellular iron to replicate. Disease states characterized by high body stores of iron increase virus replication.
6. Iron dysregulation is a key feature of severe COVID-19 infection. Altered iron balance favoring excess reactive iron may be the most important underlying pathological process predisposing to severe COVID-19 infection.
7. Air pollution is the greatest environmental health threat and one of the most important causes of the global pandemic of noncommunicable disease.
8. There is growing evidence that particulate air pollution is a potential means of transmission of COVID-19, and that it

- exacerbates susceptibility and severity of the disease.
9. There are many similarities between inflammation caused by particulate matter in air pollution and inflammation caused by COVID-19.
 10. Fine particulate matter derived from combustion sources deliver the most potent and harmful elements of air pollution. The most adverse effects are due to reactive organic particles and transition metals like iron.
 11. The recent finding of countless magnetic combustion-derived spherical nanoparticles in human brains, hearts, and placentas is definitive proof of the universal contamination of humanity by the iron oxide/magnetite fraction of air pollution.
 12. The combustion-derived magnetic particles found in human tissue and cells match the iron-magnetite ultrafine particles in coal fly ash and diesel fumes.
 13. The main sources of magnetite nanoparticles are from coal combustion, vehicle emissions, and coal fly ash utilized in global covert, undisclosed tropospheric aerosol geoengineering.
 14. Magnetic combustion-derived nanoparticles in tissue and cells cause oxidative stress and mitochondrial dysfunction. They contribute to the development and progression of cardiovascular and neurologic disease.
 15. Magnetite nanoparticles affect both cellular and humoral immunity.
 16. The intracellular toxicity of iron oxide and other nanoparticles may be related to mitochondrial dysfunction and endoplasmic reticulum stress.
 17. Coronavirus spike protein also produces endoplasmic reticulum stress.
 18. Exogenous magnetite nanoparticles interact with external electromagnetic fields.
 19. Exposure to nanoparticulate iron is “womb to tomb,” and cumulative over time.
 20. Diseases characterized by iron excess/dysregulation including obesity, cardiovascular disease, and diabetes are among the most important co-morbid conditions predisposing to severe COVID-19 infection.
 21. Ultrafine pollution particles from combustion sources have recently been found in human sera and pleural fluid.
 22. The same fine and ultrafine particles that adversely affect human health are key

elements of climate change and global warming.

23. Climate change, air pollution, and noncommunicable disease are the greatest threats to human and environmental health, and they are all intertwined and interrelated.
24. The global spread of COVID-19 is linked to these same factors. The control of COVID-19 will depend not only on global public health initiatives and therapeutics, but environmental measures as well.

14. CONCLUSIONS

Iron is necessary for DNA/RNA synthesis and it is an essential element for all organisms including viruses. However, free (non-bound), reactive iron within cells and tissue is responsible for iron's redox toxicity. For these reasons complex systemic and intracellular mechanisms are needed for proper iron handling, storage, transfer, and metabolism. There is limited excretion of iron, whereas iron can be loaded by ingestion, transfusions, disease states, and exogenous sources. Iron excess and iron dysregulation are associated with a wide variety of acute and chronic human diseases.

There is an emerging paradigm of severe COVID-19 infection as a multi-system, antibody and immune complex-mediated disease. There is evidence of antibody-dependent enhancement (ADE) of infection with COVID-19, suggesting that low (affinity) quality or quantity of antibodies will worsen rather than protect against the disease. Iron dysregulation is a key feature of severe COVID-19 infections. Covid-19 immunopathology is characterized by iron dysregulation. The most common co-morbid conditions associated with severe COVID-19 infection, for example, obesity, hypertension, and diabetes are related to iron overload or dysfunction.

Air pollution is the world's leading killer, and the smallest particulate matter derived from combustion sources contains the most harmful elements. It has been previously shown that countless exogenous magnetic combustion-derived spherical pollution nanoparticles accumulate in brains and hearts of children and adults from highly polluted areas. These particles are associated with heart disease and neurodegeneration. Diverse ultrafine particles including magnetite (Fe_3O_4) have also been found in human sera and pleural fluid. Collectively, these findings are consistent with

near-universal contamination of human tissue and cells with combustion-derived ultrafine and nanoparticles.

In human cells nanoparticles like magnetite tend to concentrate in organelles including mitochondria and endoplasmic reticulum. Reactive oxygen species and oxidative stress in these structures lead to miscommunication between mitochondria and ER, misfolding of proteins, and eventually cell breakdown and apoptosis. Ultrafine particles most likely produce toxicity by mitochondrial dysfunction and ER stress. Endoplasmic reticulum stress is recognized as a major contributor to various degenerative diseases. The mitochondrial-ER junction is involved in iron homeostasis, and COVID-19 attacks these same areas.

Growing evidence suggests that air pollution is a cofactor in the spread and severity of COVID-19. Ultrafine particles have major effects on the world's cloud layer, the hydrological cycle, climate change, and global warming. Magnetic particles in human tissue match those found in coal fly ash and certain diesel emissions. While traffic-related air pollution (TRAP) contributes to the particle load, this fraction is presumably eclipsed by coal fly ash from industrial sources, coal-fired power plants, and aerosolized coal fly ash used in tropospheric aerosol geoengineering. Climate change and global warming linked to particle pollution. Pandemics of air pollution, noncommunicable disease, and COVID-19 are interrelated and intertwined. They share the common feature of nanoparticle toxicity and iron dysregulation. Altogether these converging catastrophes pose an existential threat to human and environmental health.

The global nature of these problems shows they can only be tackled by international cooperation. Complacency about the dangers of air pollution and the deadly "code of silence", specifically, the subject of ongoing, "covert" geoengineering and "climate intervention" must be broken if the world is to have a realistic chance of controlling these public health emergencies. Immediate steps to be taken include:

1. There must be international study, quantification, and regulation of emissions of ultrafine air pollution
2. The "hidden in plain sight" tropospheric aerosol geoengineering operations must halt.
3. Small particle pollution from all sources including coal fired power plants, vehicle

emissions, fuel additives, and industrial sources must be curbed.

4. Full public disclosure as to the sources, nature, and extent of air-polluting activities.
5. Universal public health mandates (e.g. masks/face coverings) must remain in place until the COVID-19 crisis is brought under control.

These and other actions constitute a moral imperative if humanity, even our children, is to have a healthy or even viable future.

CONSENT

It is not applicable.

ETHICAL APPROVAL

No human or animal subjects were involved.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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