Minireview

Particulate matter inhalation and the exacerbation of cardiopulmonary toxicity due to metabolic disease

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Impact statement

The proportion of our society suffering from metabolic diseases is increasing and epidemiology suggests that they may be increasingly sensitive to environmental exposures such as air pollution. To date, the biological mechanisms responsible for this enhance susceptibility are not completely understood. This review summarizes our current knowledge regarding the effect of metabolic syndrome on the pulmonary and cardiovascular systems. Further, it provides a detailed synopsis of our present understanding of the mechanisms responsible for exacerbated adverse health outcomes observed in this susceptible subpopulation. The identification of these susceptibility mechanisms provides insight into the public health risks associated with air pollution exposure. This information is necessary for the establishment of regulatory policies that protect the most sensitive portions of our population as well as for the development of therapeutic strategies.

Abstract

Particulate matter is a significant public health issue in the United States and globally. Inhalation of particulate matter is associated with a number of systemic and organ-specific adverse health outcomes, with the pulmonary and cardiovascular systems being particularly vulnerable. Certain subpopulations are well-recognized as being more susceptible to inhalation exposures, such as the elderly and those with pre-existing respiratory disease. Metabolic syndrome is becoming increasingly prevalent in our society and has known adverse effects on the heart, lungs, and vascular systems. The limited evaluations of individuals with metabolic syndrome have demonstrated that they may compose a sensitive subpopulation to particulate exposures. However, the toxicological mechanisms responsible for this increased vulnerability are not fully understood. This review evaluates the currently available literature regarding how the response of an individual's pulmonary and cardiovascular systems is influenced by metabolic syndrome and metabolic syndrome-associated conditions such as hypertension, dyslipidemia, and diabetes. Further, we will discuss potential therapeutic agents and targets for the alleviation and treatment of particulate-matter induced metabolic illness. The information reviewed here may contribute to the understanding of metabolic illness as a risk factor for particulate matter exposure and further the development of therapeutic approaches to treat vulnerable subpopulations, such as those with metabolic diseases.

Keywords: Metabolic syndrome, cardiovascular disease, lung disease, inhalation toxicology, susceptibility, insulin resistance, dyslipidemia, diabetes, hypertension

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Introduction

Air pollution is a well-established and currently worsening issue in the United States, responsible for thousands of cases of respiratory illness and premature deaths each year.[1] While air pollution is composed of many substances, the United States monitors six primary air contaminants: particulate matter (PM), ozone, sulfur dioxide, nitrogen dioxide, carbon monoxide, and lead.[2] Each of these pollutants has been determined to be associated with adverse health outcomes in the population. PM, for instance, has been linked to lung disease, heart attacks, irregular heartbeat, aggravated asthma, decreased lung function, and a variety of respiratory symptoms including airway irritation, coughing, and difficulty breathing.[3] Standards are set by the EPA for the maximum allowance of criteria pollutants in the air, taking into consideration the increased sensitivities of vulnerable individuals.[4] However, these measures may not be sufficient to protect certain particularly susceptible subpopulations. Susceptible, in the context of this review, indicates a group more prone to the development of a health outcome or suffer from exacerbated responses following an exposure compared to individuals considered as healthy.

Specific groups are recognized as more susceptible to air pollution than the general population. Both epidemiological and *in vivo* laboratory studies have demonstrated that age impacts the adverse health outcomes associated

with air pollution exposures, with children and the elderly demonstrating susceptibility.[5–8] For instance, children who are exposed to higher levels of air pollution have increased asthmatic and allergic symptoms and decreased lung function as compared to children who have lower exposures.[9,10] Unsurprisingly, those who have pre-existing respiratory conditions, such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis have also been determined to be more susceptible to air pollution-induced health effects.[11–13] Together, these groups are well-known as susceptible subpopulations; the EPA acknowledges that children, the elderly, and those with respiratory diseases are at increased risk. However, those with metabolic syndrome (MetS), while demonstrating more susceptibility to adverse health outcomes as a result of air pollution, have been largely unacknowledged as a vulnerable subpopulation. MetS affects over one-third of the United States population, and its prevalence is increasing domestically and worldwide.[14–16] MetS is diagnosed when an individual exhibits three or more of the following characteristics: central obesity (increased waist circumference), hypertension, hyperglycemia/insulin resistance, high triglycerides, and dyslipidemia.[14] MetS impacts every part of the body and has a significant detrimental impact on overall health. Those with MetS are at increased risk for developing other illnesses, including renal disease, diabetes, cardiovascular disease, and certain cancers.[17–20] MetS has been determined to increase the susceptibility of individuals to adverse health outcomes following certain inhaled exposures, such as carbon monoxide and cigarette smoke.[21,22] MetS causes individuals to be more vulnerable to health outcomes such as cardiovascular depression, decreased heart rate variability (HRV), and altered cardiac repolarization as a result of inhaled PM.[23–25] While reviews have previously been published on MetS and air pollution, they have primarily focused on PM exposure as a contributing factor to the development of metabolic disease, such as MetS.[26,27] The effects of PM exposure in those who already suffer from metabolic disease, as well as the associated causal mechanisms and systemic and organ-specific impacts, are not fully elucidated.

Our current mini-review focuses on the relationship between air pollutants, MetS, and conditions associated with MetS (hypertension, dyslipidemia, and diabetes). Specifically, this review will discuss how PM exposure contributes to the development and exacerbation of local and systemic metabolic health problems, including but not limited to the heart, vascular system, and lungs. Areas which require additional research to further the existing scientific knowledge will be highlighted throughout.

Particulate matter and MetS development

It is well known that exposure to PM and other forms of air pollution is a risk factor for the development of numerous diseases. The causal link between air pollution and metabolic disease has been supported by mechanistic *in vivo* and *in vitro* laboratory studies. These evaluations have demonstrated the contribution of PM exposure to the development of metabolic disease. Specifically, PM has been observed to interfere with glycogen storage, resulting in altered glucose metabolism and disrupted insulin homeostasis.[28] This is in part due to the impaired cellular signaling that occurs as a result of PM exposure, such as the suppression of insulin receptor substrate 1 and the reduction of phosphorylated protein kinase B, which prevents the effective uptake and utilization of glucose and thus contributes to the development of insulin resistance.[28–30] The alteration of glucose metabolism contributes to the development of metabolic disease, with insulin resistance being one of the key components of MetS. Additionally, exposure to PM has been demonstrated to cause inflammation and alter the expression of genes associated with MetS, such as tumor necrosis factor-α (TNF- α), interleukin 6, and β,β-carotene-9′,10′-oxygenase 2.[30–32] This inflammatory response, in combination with the oxidative stress induced by PM exposure, has been determined to be a contributing factor to the development of dyslipidemia, a key characteristic of MetS.[33] These primary adverse health outcomes caused by PM exposure have also been observed to contribute to the development of secondary problems frequently concurrent with MetS, such as non-alcoholic hepatic steatosis.[28] Multiple reviews have been published on this subject which further detail the mechanistic link between PM exposure and metabolic disease development.[26,27,34] It is clear that PM exposure does not cause MetS through a singular mechanism, but rather by the disruption of multiple systems and signaling pathways, creating a complex network of dysfunction.

The ultimate outcome of this dysfunction in human populations has been the subject of much research. Multiple epidemiological studies have linked ambient PM exposure to metabolic disease. Even relatively brief sub-acute exposures to low concentrations of PM have been observed to reduce insulin sensitivity in human subjects.[35] As one would expect, longer exposures and higher PM concentrations are associated with more severe effects. Proximity to major roadways is associated with a higher prevalence of non-alcoholic hepatic steatosis, likely due to the exposure to higher concentrations of PM.[36] Studies which have examined the effects of long-term PM exposure on humans have identified an association between PM inhalation and MetS, with one study finding a 72% increase in MetS per 10 $\mu g/m^3$ increase in mean PM.[37] Other researchers have performed more thorough analyses, examining not only MetS, but its components and associated conditions. Hyperglycemia, dyslipidemia, obesity, and hypertension have all been determined to be associated with PM exposure.[38,39] The impact of PM on the development of MetS and its associated conditions is well-established; however, metabolic disease as an aggravating factor contributing to the exacerbation of the adverse effects of air pollution is less well studied.

Pulmonary effects associated with MetS and PM exposures

Inhalation is the primary route of exposure for air pollutants, making the pulmonary system particularly

susceptible to adverse health outcomes. Once inside the lungs, PM can interact with the cells and tissues of the lung itself, causing local inflammation.[40] Particles may also translocate from the lungs to the circulation to cause systemic effects throughout the body, with smaller particles doing so with greater efficiency than larger particles.[41]

MetS and lung function

It is well established that MetS impacts lung function; MetS has been shown to decrease forced expiratory volume (FEV_1) and forced vital capacity independent of factors such as smoking status and alcohol consumption.[42] Additionally, MetS is associated with various lung and breathing disorders, including asthma, obstructive sleep apnea, as well as resting and post-exercise dyspnea.[43–45] The exact mechanism by which MetS leads to lung disorders is not fully understood; however, previous research has demonstrated that exposure to excess levels of insulin may induce hypercontractility in the smooth muscle of the airway and bronchoconstriction through the phosphoinositide 3-kinase/rho kinase pathways and the loss of muscarinic receptor 2 functionality, respectively.[46–48] The role of insulin in decreased lung function is also supported by epidemiological data; the National Health and Nutrition examination survey has provided evidence of a link between insulin and decreased lung function, with insulin resistance being inversely associated with FEV_1 and forced vital capacity (FVC).[49] Interestingly, the detrimental effect of excess insulin on the lungs is not exclusive to adults. Exposure to high levels of insulin during development has been demonstrated to delay fetal lung development through the inhibition of surfactant protein A and B genes, which is likely a contributing factor in a higher incidence of infants with respiratory distress syndrome and asthma born to diabetic mothers.[50–52] It has been proposed that the altered pulmonary function caused by MetS results in disordered breathing during sleep, increasing the levels of pro-inflammatory cytokines present in the body and resulting in a positive feedback loop, in which the conditions of MetS cause disordered breathing during sleep, and the hypoxic conditions caused by disordered breathing in turn worsen MetS and thus perpetuate the cycle.[53] Other components of MetS have been observed to alter lung function, as well. Obese individuals have decreases in FEV_1, FVC, total lung capacity, and residual volume.[54] A reduction in functional residual capacity is well-documented to occur even at modest weight increases, and is thought to be the result of adipose tissue in the abdomen placing pressure on the chest wall.[55] Hypertension and dyslipidemia have also been determined to be associated with lung disease and functional pulmonary decline, though the mechanisms behind these associations is not thoroughly understood[56–58] It is clear that the impact of MetS on lung function is both adverse and cyclical, with metabolic and breathing problems contributing to and exacerbating one another. Even in the absence of external factors, these factors would present a significant health issue to those affected by MetS, but unfortunately, these issues do not occur in isolation, and individuals with MetS must contend with an additional problem: air pollution.

Metabolic disease as an aggravating factor

A limited number of studies have been performed specifically addressing the impact of MetS as a susceptibility factor increasing health outcomes resulting from PM exposure. However, more studies have examined the role of distinct components of MetS and their individual capacity to alter PM-induced pulmonary toxicity and enhance vulnerability. Of these, hypertension is perhaps among the most well-studied. Several *in vivo* laboratory studies have demonstrated that hypertensive animals are more susceptible to adverse pulmonary health outcomes as a result of the effects of PM. These adverse health outcomes include but are not limited to increased inflammation, oxidative stress, bronchoalveolar lavage fluid protein, edema, thickening of the alveolar wall, and hemorrhage to alveolar parenchyma, all of which have the potential to cause deficits in lung function.[59,60] TLR-4 cell signaling is likely partially responsible for these lung problems, as it is known to promote the inflammatory response and has been observed to be enhanced in hypertensive rats following PM inhalation.[61] Enhanced ventilatory dysfunction has also been observed in hypertensive conditions following exposure to PM.[62] This has been supported by epidemiological studies, which have shown that hypertensive individuals have an altered reaction to PM exposure compared to healthy individuals. Specifically, exposure to PM is associated with a decrease in 8-hydroxy-2′-deoxyguanosine in hypertensive individuals compared to an increase in non-hypertensives, possibly indicating that hypertension impairs the ability to repair oxidative DNA damage.[63] Combined, these results indicate that hypertension, a disease commonly associated with MetS, increases individuals' susceptibility to adverse pulmonary health outcomes as a result of PM exposure.

Other MetS-associated conditions have been determined to increase susceptibility to PM exposure, as well. Cardiomyopathy, similarly to hypertension, has been determined to increase individuals' vulnerability to PM exposure, exacerbating pulmonary inflammation and injury.[64] Obesity is associated with increased wheezing and a decline in lung function in those exposed to PM.[65] In patients with pre-existing respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD), obesity is associated with increases in the frequency or severity of symptoms, such as dyspnea.[66,67] This enhanced vulnerability as a result of excess weight is likely due in part to the innate hyperresponsiveness of the airway in obesity.[68] Diabetes, which frequently occurs as a result of or in conjunction with MetS, has also been observed to sensitize individuals to PM exposure. Studies have observed increased apoptosis, oxidative stress, and inflammation in the lung in a mouse model of diabetes exposed to PM.[69,70] These effects, when present in the clinical setting, are often linked with increased mortality. There is an approximately two-fold increase in the risk of respiratory and stroke-related deaths in the presence of diabetes,

which researchers suggest may be due to impaired vascular function.[71] Finally, lipid dysregulation inherent to MetS is likely a contributing factor in their increased susceptibility, as patients with dyslipidemia have been demonstrated to be at increased risk of developing COPD due to air pollution.[72]

Though the mechanism responsible for this increased susceptibility is not well understood, it may be in part due to increased lung inflammation which is observed in hypercholesterolemia.[73] Additionally, this may lead to exacerbated systemic effects, as pulmonary inflammation has been determined to enhance particle translocation from the lungs to the circulation.[74] Pulmonary inflammation itself is enhanced in MetS, as well. A recent study of the effect of particles in the lung using both healthy and MetS mouse models demonstrated that MetS mice had not only an exaggerated inflammatory response to exposure, but decreased levels of specialized pro-resolving mediators.[75] This suggests that MetS may not only result in exacerbated pulmonary effects, but also an impairment of inflammatory resolution, prolonging the inflammatory response and contributing to disease development. Regarding the impact of MetS specifically in humans, lung injury, airway hyperreactivity, and decreases in lung function have been determined to be more common in individuals who suffered from MetS around the time their exposure to dust generated by the destruction of the United States World Trade Center.[76–78] These effects persisted even 16 years after exposure, and will likely affect exposed individuals for the remainder of their lives. Furthermore, individuals with biomarkers of inflammatory or cardiovascular disease such as macrophage-derived chemokine, granulocyte-macrophage colony-stimulating factor, lysophosphatidic acid, or apolipoproteins AI, CII, and CIII have also been determined to have increased risk of lung injury and impaired lung function as a result of exposure.[79–81]

Multiple other mechanisms have been proposed to explain the increased risk of the development and exacerbation of pulmonary illness. Increased protein turnover in MetS may lead to reduced bioavailability of arginine and reduced nitric oxide production, resulting in epithelial damage and dysfunction.[82] A study of MetS in combination with an allergic mouse model demonstrated the presence of dysfunction and stressed mitochondria in the bronchial epithelium, which resulted in airway hyperreactivity even with no allergen present.[83] Chemokine (C-X-C motif) receptor 3 also likely plays a role in the increased vulnerability of individuals with MetS, as it is known to be involved in allergic airway inflammation and has been demonstrated to modulate diet-induced insulin resistance and macrophage infiltration in visceral adipose tissue.[84,85] Lipid dysregulation may also contribute to the exacerbation of pulmonary dysfunction, as both metabolic disease and PM inhalation have been determined to alter lipid profiles and metabolism[86–88] Given that lung surfactant is composed of 90% lipids by mass, alteration of lipid metabolism has the potential to significantly impact lung function and disease, with overproduction, underproduction, and changes to surfactant composition all being associated with illness.[89] While MetS itself has been the topic of few studies examining increased susceptibility, research of its components and associated diseases has demonstrated that individuals with MetS are more vulnerable to adverse pulmonary health outcomes as a result of PM air pollution. This enhanced susceptibility associated with MetS and its associated should be taken into account when affected individuals enter areas which are known to have elevated levels of PM air pollution. These individuals likely require additional safety measures, such as reduced time outdoors during high pollution days. Further, these findings suggest that physicians may need to consider supplemental screening of individuals with MetS following exposures to detect PM-associated diseases at earlier stages.

Conclusions

While further research is needed to elucidate biological mechanisms of increased susceptibility to PM exposure due to metabolic disease, it is likely excess levels of insulin present in MetS contribute by inducing airway hypercontractility and bronchoconstriction. There is also evidence to suggest that metabolic disease and PM inhalation aggravate one another through inflammatory mechanisms and the dysregulation of lipid metabolism. It is likely that the increased sensitivity of individuals with MetS is due to a combination of the above listed factors, as well as others yet to be discovered. One of the most conspicuous gaps in our current knowledge is the comparative lack of studies on lipid mediators of inflammation. Underlying diseases that alter lipids, such as MetS, may cause deficient resolution signaling resulting in exacerbated and extended pulmonary inflammation. Furthermore, modulation of lipids may be a potential therapeutic target for treatment of pulmonary issues in individuals with MetS exposed to PM. Additional research is required to gain a more complete understanding of the complex interactions between PM, MetS, and pulmonary illness.

Cardiovascular effects associated with MetS and PM exposures

While the pulmonary system is directly exposed to inhaled air pollutants, the cardiovascular consequences may be the most concerning and also exacerbated due to MetS. The relationship between PM exposure and cardiometabolic disease is robust, and is demonstrated by well-documented associations with cardiac arrhythmia, hypertension, atherosclerosis, myocardial infarction, and ischemic stroke.[90–94] Due to the increased risk of cardiovascular events, the effects of PM on the cardiovascular system have been the subject of many studies. A number of mechanisms have been proposed to explain the impact of PM on the cardiovascular system, including direct translocation of particles to the circulation, the induction of pulmonary oxidative stress and systemic inflammation, and triggering of autonomic nervous system responses.[95–99]

Cardiovascular dysfunction resulting from MetS

The impact of metabolic disease on cardiovascular function is significant and well-documented. Multiple studies have

established that MetS is associated with an increased risk of cardiovascular disease and mortality.[19,100,101] Specifically, MetS is related to a number of cardiovascular conditions, including microvascular and cardiac dysfunction, coronary calcification, myocardial infarction, and heart failure.[102–106] In terms of cardiovascular function, MetS causes alterations in heart rate, cardiac output, and vascular resistance, creating a hemodynamic phenotype with a higher risk of cardiovascular disease (CVD).[107–109] A number of mechanisms are thought to contribute to the increased cardiac vulnerability seen in MetS, with one of the most prominent being the altered handling and storage of calcium ions (Ca^{2+}). This is thought to occur primarily through impaired function of ryanodine receptors and altered activity of the cardiac sarco(endo)plasmic reticulum Ca^{2+} ATPase (SERCA2) protein.[110] Type 2 ryanodine receptors (RyR2) act as the major release channels through which Ca^{2+} exits the sarcoplasmic reticulum in the heart, causing cardiac muscle contraction.[111] Phosphorylation of RyR2 is enhanced in MetS, and binding affinity is reduced.[112] This causes the RyR2 channels to be "leaky," leading to disrupted calcium homeostasis and contributes to impaired contraction, ventricular arrhythmia, and heart failure.[113] The role of SERCA2 in increasing individuals' susceptibility to CVD is less well understood. In healthy individuals, SERCA2 transfers Ca^{2+} from the cytosol to the sarcoplasmic reticulum, regulating muscle contraction through the maintenance of normal Ca^{2+} levels.[114] However, in MetS conditions, the activity of SERCA2 is reduced, leading to impaired Ca^{2+} uptake and contractile dysfunction.[115] There is conflicting research regarding the exact mechanism by which SERCA2 activity is reduced; while some studies indicate that the reduced functionality is likely due to decreases in protein expression, others have demonstrated a decrease in activity with no change in expression.[106,115,116] Evidence suggests that the reduced activity of SERCA2 in MetS is not driven solely by protein abundance, and may be due partially to oxidative-stress induced structural changes.[117] While the altered activity of SERCA2 and RyR2 are core elements of the MetS-induced electrophysiological cardiac dysfunction, myocardial titin, which controls muscle elasticity in the sarcomere, is also a probable mediator.[106,118] In an animal model of metabolic disease, titin was determined to be hyperphosphorylated, increasing cardiac muscle stiffness and contributing to heart failure.[119] This finding has been supported by human studies, as well; patients with hypertension and diastolic heart failure have been determined to have altered myocardial titin phosphorylation and increased titin-dependent stiffness when compared to controls.[120] Metabolic disease even goes as far as to alter the metabolism of the myocardium itself; with obesity causing increased cardiac uptake and oxidation of fatty acids.[121] This has been observed in animal models, as well as humans with obesity, insulin resistance, and diabetes.[122–124] This increased uptake and utilization of fatty acids as an energy source is not without consequence, and causes an increase in insulin resistance and reactive oxygen species while also decreasing cardiac efficiency.[125,126] The mechanisms described here are not an exhaustive list, as the link in between metabolic disease and CVD is complex and has been the topic of multiple reviews.[127–129] The exacerbation of CVD as a result of MetS is likely not the result of any one specific mechanism, but rather a variety of pathways contributing to cardiac dysfunction and illness.

MetS as an aggravating factor

By itself, PM exposure is known to increase individuals' susceptibility to adverse cardiovascular outcomes.[130] Given this, a significant amount of research has been performed to determine if metabolic disease, which also negatively impacts cardiovascular function, acts as an additional risk factor.[131,132] Toxicological studies in animal models have determined that MetS predisposes individuals to greater cardiovascular dysfunction following PM inhalation, including decreased HRV, increased arrhythmia, and depressed heart rate and blood pressure.[25,133] Interestingly, this is likely not the result of any direct effects of PM on the cardiovascular system itself, but rather lung-mediated activation of the autonomic nervous system. Exposure to PM induces increased production of norepinephrine in the hypothalamus of insulin-resistant obese rats, more so than in healthy animals.[134] This norepinephrine acts as an agonist of the α2 adrenoceptor, which has been shown to be sensitized to respond to ligands due to MetS.[135,136] It is likely that the increased baseline sensitivity of the adrenoceptor in combination with increased agonist stimulation by norepinephrine results in a high level of receptor responsiveness. The resulting increased activation of the α2 adrenoceptor decreases the activity of the sympathetic nervous system, and thus alters cardiac function.[136,137] Interestingly, α2 adrenoceptor agonists have been used to treat sympathetic nervous system hyperactivity, which can also cause cardiac dysfunction.[138] The capacity of metabolic disease to worsen cardiovascular health outcomes is seen in humans as well, with alterations observed in cardiac function as well as biomarkers of cardiovascular health. Specifically, PM has been demonstrated to cause decreases in plasminogen and thrombomodulin, and increases in C-reactive protein, serum amyloid A, and white blood cell count (WBC).[23,24,139] This is indicative of an acute phase response, demonstrating a systematic response to inhaled exposures. Decreased HRV and altered cardiac rhythm have also been observed to be exacerbated in individuals with MetS.[24,140] Plasminogen and thrombomodulin are both involved in the fibrinolytic pathway, indicating that MetS could potentially lead to worse cardiovascular health outcomes as a result of impaired breakdown of blood clots.[141,142] C-reactive protein, serum amyloid A, and WBC are all well-established biomarkers of heart disease, with all being indicative of widespread inflammation.[143–145] Reduced HRV has not only been linked to an increased risk of cardiovascular events, but also an increased risk of mortality.[146,147] The evidence would appear to overwhelmingly indicate that MetS presents a clear additional risk for those exposed to PM, but paradoxically, one of the largest studies to date of the relationship between MetS and PM has demonstrated exactly the opposite. A nationwide prospective cohort study of over 669,000

individuals concluded that metabolic disease does not increase the risk of PM-induced cardiovascular mortality.[148] However, the researchers concede that a number of issues exist in their study which may have confounded the results, including imperfect classification of pre-existing conditions and a biased sample pool, which included a disproportionate number of well-educated, affluent individuals and was not representative of the population at large. Further, the researchers speculate that rather than directly increasing the risk of cardiovascular mortality as a result of exposure, metabolic disease may have instead been exacerbated by PM inhalation, leading to ancillary health effects. In light of this seemingly contradictory laboratory and epidemiological evidence, additional studies are needed to clarify the impact of MetS on the cardiovascular health outcomes associated with PM inhalation.

While further research is required to determine the capacity of MetS to increase individuals' susceptibility to PM exposure, several associated components of MetS have abundant evidence supporting their ability to worsen cardiovascular health following PM exposure. *In vivo* studies have demonstrated that individuals with hypertension are more prone to a variety of cardiovascular issues following PM inhalation, including depressed heart rate and blood pressure, increased WBC, and dysrhythmia.[60,149–151] The increased impact of PM in such conditions has been supported by epidemiological studies of human populations, which have observed decreased HRV as well as increased rates of doctor visits for dysrhythmia and heart failure in hypertensive individuals.[152,153] Biomarkers of heart disease, including C-reactive protein (CRP) and WBC, are also observed to be increased in hypertensive individuals as compared to healthy following PM inhalation.[154] Similar effects have been observed in obesity, with greater increases seen in the levels of CRP and WBC.[154,155] Interestingly, elevations have also been observed in soluble vascular cell adhesion molecule (sVCAM-1).[156] SVCAM-1 is an immunoglobulin-like marker of inflammation and endothelial function that binds integrins found on the surface of monocytes, thus allowing for monocytic migration into the vessel wall.[157–159] This likely indicates that obese individuals are at a greater risk of developing or worsening arterial disease as a result of PM exposure, as this process is crucial to the development of atherosclerosis.[160] Functional deficits have also been observed in obesity, including decreases in HRV and endothelial function.[161,162] Unsurprisingly, these biological and functional alterations have a tangible effect on the health of those affected. Obesity significantly increases the risk of experiencing a cardiovascular event, such as myocardial infarction, as a result of PM exposure.[163] While fewer studies have been performed regarding the impact of diabetes on the cardiovascular effects of PM exposure, those which do exist indicate a decidedly negative influence. Diabetes has been determined to worsen the biochemical and functional physiological changes associated with PM exposure, increasing CRP and WBC levels and as well as the risk of dysrhythmia.[153,154] This is likely due at least in part to the PM-induced exacerbation of cardiomyocyte dysfunction which is observed in diabetic conditions. Specifically, PM has been determined to inhibit the sarcomere contractile properties of cardiomyocytes, which already experience a functional decline due to the presence of excess glucose.[164] The production of reactive oxygen species is likely at least partially responsible for this additional decline, as markers of oxidative stress such as 8-hydroxydeoxy-guanosine are elevated in diabetic conditions following PM exposure, and antioxidants have a restorative effect.[164,165] Epidemiological studies have determined the real-world impact of the increased vulnerability of this subpopulation; diabetics are twice as likely to be admitted to the hospital for PM-induced cardiovascular events or diseases.[166] Dyslipidemia is perhaps the most studied MetS-associated condition regarding its impact on the cardiovascular effects of PM exposure. Perhaps the most impactful effect PM has on cardiovascular health is its well-documented ability to worsen atherosclerosis, increasing the size and number of plaques present, as well as altering their composition.[167–172] Some of these alterations make the plaques more susceptible to rupture, an event which causes thrombosis and can lead to eventual oxygen deprivation and myocardial infarction.[171,173] Mechanistically, the enhanced progression of atherosclerosis is likely due to a number of factors, including expression of pro-inflammatory and oxidative stress markers such as visfatin, TNF-α, iNOS, and others.[167,170,172,174] This in turn leads to increased expression of cell adhesion molecules such as vascular cell adhesion molecule-1, enhancing monocytic migration, and worsening atherosclerosis.[172,175] Changes in cardiac function are observed in dyslipidemia, as well, such as decreases in HRV and heart rate.[176,177] It is clear that both MetS and its associated conditions have the capacity to exacerbate PM-induced cardiovascular system effects.

Conclusions

The cardiovascular system is sensitive to the effects of inhaled PM that may be enhanced due to MetS. The advancement of atherosclerosis following PM exposure in MetS may be the most significant toxicological outcome. While additional research is needed to establish mechanisms by which MetS itself constitutes an additional risk factor for PM exposure, the evidence indicates that the associated disorders of hypertension, obesity, diabetes, and particularly dyslipidemia do increase an individual's risk for adverse cardiovascular outcomes following PM inhalation.

Hepatic and developmental effects

It is apparent based on both the epidemiological and mechanistic laboratory research that metabolic disease has the capacity to worsen adverse cardiovascular and pulmonary health outcomes that occur as a result of PM exposure. Individuals who suffer from MetS and other metabolic illness are more susceptible to the development or worsening of diseases such as asthma and atherosclerosis, potentially increasing the risk of mortality. While the pulmonary and cardiovascular systems are the focus of this review, it should be emphasized that PM has systemic effects on multiple organ systems throughout the body. Non-alcoholic

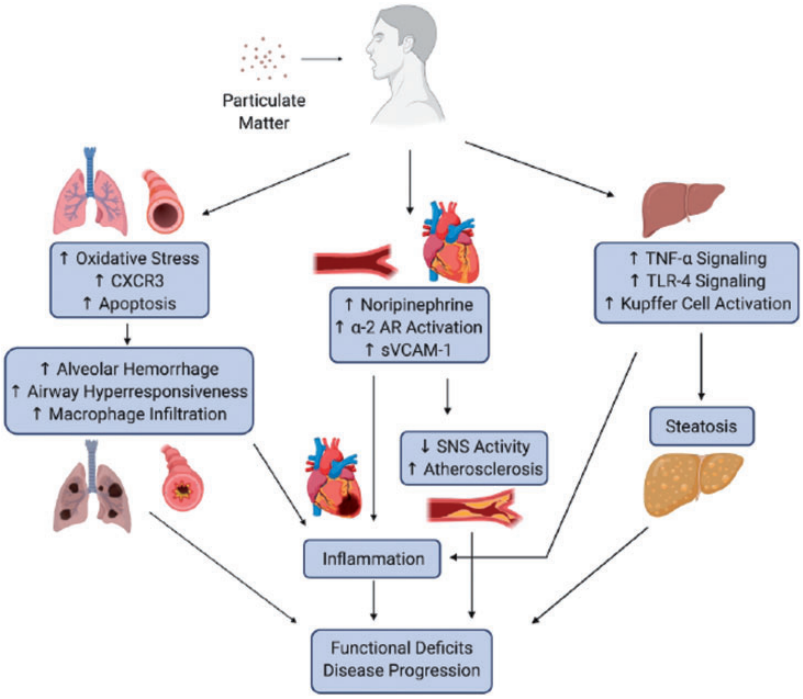

Figure 1. Mechanistic pathways and pathological effects of inhaled particulate matter on the pulmonary, cardiovascular, and hepatic systems (Figure created with Biorender.com). (A color version of this figure is available in the online journal.)

fatty liver disease (NAFLD), a condition frequently considered to be a component of MetS, is thought to be aggravated by exposure to PM.[178] MetS models have been shown to be more susceptible to lipid accumulation following particle exposure, contributing to the development of steatosis.[179] Additionally, a greater overall decrease in liver function has been observed in mouse models of metabolic disease following PM exposure, with lowered ALT and AST, enhanced steatosis, and increased levels of hexanoyllysine, a marker of oxidative stress.[180] While the mechanisms responsible for this increased vulnerability are not fully understood, it is thought that inflammation plays a large role. Reduction of TNF-α signaling through the use of an inactive rhomboid protein 2 knockout model significantly attenuated PM-induced dyslipidemia and hepatic injury.[181] Further, PM inhalation has been demonstrated to induce TLR-4 dependent activation of Kupffer cells, increasing pro-inflammatory cytokine production and potentially exacerbating NAFLD.[178] It is likely that the inflammation and TNF-α signaling caused by PM are partially responsible for the TLR activation of Kupffer cells, and thus the worsening of metabolic liver disease. The effects of PM are in fact so far-reaching that they may influence the development of metabolic disease even before birth. Maternal inhalation of fine PM has been demonstrated to predispose offspring to the development of MetS.[182] Specifically, rat studies have shown that pups that are born to mothers that were exposed to fine PM not only suffer from impaired organogenesis, but disrupted lipid and glucose homeostasis, elevated hepatic lipids, and increased plasma glucose and fatty acids concentrations in adulthood.[183] A similar association has been observed in human newborns as well; exposure to PM during pregnancy has been determined to be associated with higher levels of cord plasma insulin, potentially indicating an increased risk of glucose intolerance and metabolic disease later in life.[184]

Potential interventional approaches to mitigate MetS-associated exacerbations

The effects of PM on the body are systemic and adverse. The inhalation of PM can contribute to the development or exacerbation of metabolic disease, reducing not only individuals' lifespans, but their quality of life as well. Fortunately, research has indicated a number of methods that may attenuate the negative impact of PM exposure. Physical activity has been determined to have a negative association with MetS, though its protective effect is reduced at higher ambient PM concentrations.[185] A variety of medications have also demonstrated effectiveness at reducing the metabolic effects of PM inhalation. Treatment with hydralazine, a medication used to reduce blood pressure, reduced PM-induced pulmonary leakage in exposed rats, though it did not alter neutrophilic inflammation or lung injury.[186] Statin medications have also been determined to potentially have a protective effect, attenuating the development of atherosclerosis and endothelial dysfunction induced by PM exposure.[187] One study determined that a statin treatment inhibited the exacerbated particle-induced acute inflammatory response observed in MetS, with a corresponding inhibition of alterations in specialized pro-resolving mediators.[75] Together, these findings suggest that statins may modulate the induction and resolution of the inflammatory response and be protective against the development and exacerbation of MetS and its associated conditions.

Overall conclusions

While the associations between PM exposure and metabolic illness are clear, the mechanisms responsible are still largely undetermined. This is likely due, at least in part, to the complexities of the interactions between the multiple organ systems impacted by PM, as illustrated in Figure 1. While this review focused primarily on the impact of PM on the pulmonary and cardiovascular systems, the effects are in fact systemic, impacting every system in the body. Inflammation, oxidative stress, and insulin resistance have all been implicated in the susceptibility of individuals with metabolic illness, and it is likely the interaction between these and other factors which is the cause of the enhanced vulnerability. Physical activity and medication have been demonstrated to have protective effects, but additional research is necessary to understand both the mechanisms underlying the increased sensitivity of those with metabolic illness, and the most effective way to protect this vulnerable subpopulation. By understanding the mechanisms by which PM exposure contributes to the development and progression of MetS and Met-associated diseases, intervention strategies for these conditions may be developed and implemented to assist with the treatment of the underlying condition, as well as any complications which may arise as a result of PM exposure.

AUTHORS' CONTRIBUTIONS

All authors participated in the conceptualization of the manuscript. LK performed the literature review, as well as writing, and editing. JS assisted in outlining and editing, as well as contributed to revisions of the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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