

Review

# Metabolic Syndrome and Air Pollution: A Narrative Review of Their Cardiopulmonary Effects

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**Abstract:** Particulate matter (PM) exposure and metabolic syndrome (MetSyn) are both significant global health burdens. PM exposure has been implicated in the pathogenesis of MetSyn and cardiopulmonary diseases. Individuals with pre-existing MetSyn may be more susceptible to the detrimental effects of PM exposure. Our aim was to provide a narrative review of MetSyn/PM-induced systemic inflammation in cardiopulmonary disease, with a focus on prior studies of the World Trade Center (WTC)-exposed Fire Department of New York (FDNY). We included studies (1) published within the last 16-years; (2) described the epidemiology of MetSyn, obstructive airway disease (OAD), and vascular disease in PM-exposed individuals; (3) detailed the known mechanisms of PM-induced inflammation, MetSyn and cardiopulmonary disease; and (4) focused on the effects of PM exposure in WTC-exposed FDNY firefighters. Several investigations support that inhalation of PM elicits pulmonary and systemic inflammation resulting in MetSyn and cardiopulmonary disease. Furthermore, individuals with these preexisting conditions are more sensitive to PM exposure-related inflammation, which can exacerbate their conditions and increase their risk for hospitalization and chronic disease. Mechanistic research is required to elucidate biologically plausible therapeutic targets of MetSyn- and PM-induced cardiopulmonary disease.

**Keywords:** particulate matter; systemic inflammation; metabolic syndrome; chronic obstructive pulmonary disease; cardiovascular disease; blood pressure; World Trade Center

## 1. Introduction

Cardiopulmonary disease caused by ambient particulate matter exposure accounts for 7 million deaths globally each year [1–3]. Epidemiologic associations have been documented between increased ambient particulate matter (PM), lung disease, and cardiovascular disease (CVD) [4–11]. The aim of this review article is to provide an up-to-date overview of the epidemiological and biological mechanism of PM-induced systemic inflammation in MetSyn, obstructive lung disease, and CVD. This review also discusses the contribution of PM exposure and MetSyn to cardiopulmonary disease. A cohort of firefighters that was exposed to World Trade Center Particulate Matter (WTC-PM) has been identified as having metabolically active biomarkers associated with the development of WTC-lung

injury (WTC-LI) [12–18]. We also specifically discuss the relationship between PM exposure and MetSyn in the WTC-exposed FDNY firefighters.

## 2. Review/Search Strategy

PubMed databases were searched in July and August of 2018. The search was also limited to articles that were published within the last 16 years, from January 2002 to August 2018. Cohort studies, case control studies, narrative reviews, meta-analyses, and mechanistic and statistical summaries were retrieved. Titles, abstracts, and full texts were screened based on relevance to this review. Keywords searched included: “obstructive airway disease”, “asthma”, “air pollution”, “particulate matter”, “occupational exposure”, “World Trade Center”, and “chronic obstructive pulmonary disease.” In addition, the references of many of the articles identified by the above search strategy were reviewed.

### *Inclusion/Exclusion Criteria and Limitations*

Studies were included in our narrative review if they: (1) described the coexistence of MetSyn, cardiopulmonary disease and PM exposure, (2) detailed the mechanisms of PM-induced inflammation within these diseases, or (3) focused on the effects of PM-exposure in WTC-exposed FDNY firefighters. We included (4) observational, retrospective, systematic reviews or clinical studies that focused on: (5) providing the epidemiology and etiology of PM and associated MetSyn and cardiopulmonary disease, or (6) the use of biomarkers to evaluate environmentally associated MetSyn and cardiopulmonary disease.

Studies were excluded if they: (1) were not included in PubMed, (2) were published earlier than 2002, or (3) were not written in the English language. Studies included in this review were available in their entirety online and were referenced using Endnote X8 (Thomson Reuters, Philadelphia, PA, USA, 2016).

Limitations of this study design include: (1) use of only the PubMed database, (2) the fact that it is not a systematic review, and therefore (3) performing a full meta-analysis of the obtained data is limited.

## 3. Epidemiological Studies

### *3.1. Epidemiology of MetSyn and PM Exposure*

MetSyn is defined as having at least three of five risk factors associated with development of cardiovascular disease, diabetes, and stroke: abdominal obesity, insulin resistance, hypertriglyceridemia, low HDL, and hypertension, Figure 1 [19].

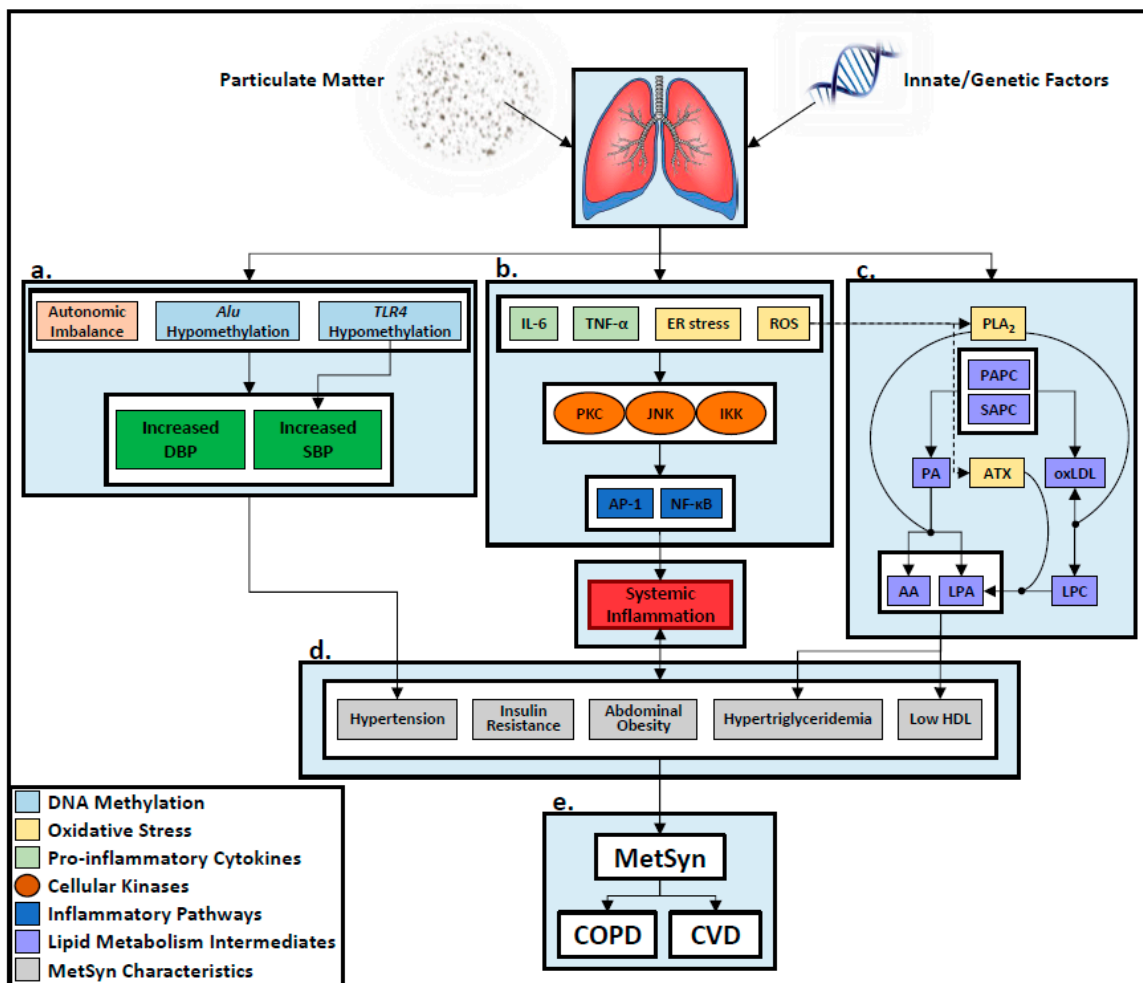
PM exposure, having been linked to developing elevated blood pressure (BP), is a risk factor for developing MetSyn characteristics, Figure 1a. PM exposure is often focused on the respirable portion of ambient air (2.5 and 10 micrometers in size). In a recent longitudinal study, adults that resided in locations with high ambient PM<sub>2.5</sub> concentrations experienced significant elevations in diastolic BP. Overweight adults living in the same area experienced increases in both systolic and diastolic BP; however, no PM<sub>2.5</sub>-related BP changes were found in locations where ambient PM<sub>2.5</sub> concentrations remained low; therefore, this study suggests increased PM<sub>2.5</sub> exposure promotes elevations in BP among healthy and obese individuals, with the latter being more susceptible to the effects of ambient air pollution [20].

Additional human studies have demonstrated that PM<sub>2.5</sub> causes an increase in BP after only a few days of exposure, and exposure over years can lead to chronic hypertension, Figure 1a,d [21]. PM inhalation also promotes the development of insulin resistance, which has been mechanistically linked to hypertension [22]. Insulin resistance, is considered the primary risk factor for diabetes mellitus [23]. A recent longitudinal study of 1,729,108 participants followed for a median of 8.5 years showed that PM<sub>2.5</sub> air pollution is significantly associated with an increased risk of diabetes, Table 1 [24].

**Table 1.** Overview of the effects of PM exposure on metabolic and cardiopulmonary diseases.

Disease	Study	Country	Study Population	Significant Findings
METSYN	Animal Studies			
	Brocato [1]	USA	Murine model	PM exposure enhances the expression of genes located in pathways associated with MetSyn.
	Wei [25]	China	Murine model	Chronic exposure to PM increases the risk of MetSyn.
	Sun [26]	USA	Murine model	Long-term PM exposure exacerbates MetSyn.
	Human Studies			
	Huang [20]	China, USA	Longitudinal cohort	High PM <sub>2.5</sub> exposure promotes BP elevations in healthy and overweight individuals.
	Bowe [24]	USA	Longitudinal cohort	Inhalation of PM <sub>2.5</sub> is significantly associated with increased risk for developing diabetes mellitus (HR, 1.15; 95% CI, 1.08–1.22).
Naveed [13]	USA	Longitudinal cohort	MetSyn biomarkers—abnormal triglycerides and HDL (OR, 3.03; 95% CI, 1.39–6.16) and elevated heart rate (OR, 2.20; 95% CI, 1.14–4.24) and leptin (OR, 3.00; 95% CI, 1.35–6.66)—are risk factors of lung function impairment after WTC PM exposure.	
COPD	Human Studies			
	Gan [27]	Canada	Population-based cohort	Exposure to particulates in traffic-related air pollution was associated with a 6% increase in the risk of COPD hospitalization (95% CI, 2–10%).
	Dominici [10]	USA	Population-based cohort	Increased PM exposure doubled hospital admissions for COPD exacerbations.
	Vujic [28]	Serbia	Cross-sectional	Systemic inflammatory markers are higher in COPD patients with MetSyn than in those without MetSyn. Individuals with MetSyn have a higher leukocyte count (OR, 1.321; 95% CI, 1.007–1.628) and C-reactive protein level (OR, 1.184; 95% CI, 1.020–1.376) compared to those without MetSyn.
Samoli [29]	Europe	Cross-sectional	PM <sub>2.5</sub> is positively associated with mortality due to diabetes (1.23%; 95% CI, 1.63–4.17%), cardiac causes (1.33%; 95% CI, 0.27–2.40%), COPD (2.53%; 95% CI, 0.01–5.14%), and to a lesser degree to cerebrovascular causes (1.37%; 95% CI, 1.94–4.78%).	
CVD	Animal Studies			
	Tankersley [30]	USA	Murine model	Carbon black exposure led to impaired cardiac function in senescent mice
	Sun [31]	USA	Murine model	Long-term PM exposure altered vasomotor tone, induced vascular inflammation, and potentiated atherosclerosis.
	Human Studies			
	Devlin [32]	USA	Case-crossover	MetSyn patients with no overt CVD experienced PM-induced cardiovascular changes.
	Park [33]	USA	Longitudinal cohort	As a result of PM exposure, individuals with MetSyn had significantly larger decreases in heart rate variability measures than those without MetSyn. Patients with MetSyn experienced a 2.1% decrease in the root mean square of successive differences (95% CI, −4.2–0.0) and a 1.8% decrease in the standard deviation of normal-to-normal intervals (95% CI, −3.7–0.1).
Chang [34]	Taiwan	Case-crossover	Short-term PM exposure increases hospital admissions for CVD. On cool days, PM <sub>2.5</sub> exposure was associated with a 47% (95% CI, 39–56%), 48% (95% CI, 40–56%), 47% (95% CI, 34–61%), and 51% (95% CI, 34–70%) increase in ischemic heart disease, stroke, congestive heart failure, and arrhythmias hospital admissions, respectively.	
Miller [35]	USA	Prospective cohort	Long-term PM exposure was related to cardiovascular disease and mortality. Each increase of 10 microgram per cubic meter of PM <sub>2.5</sub> was associated with a 24% increase in the risk of cardiovascular event (HR, 1.24; 95% CI, 1.09–1.44) and a 76% increase in the risk of death from CVD (HR, 1.76; 95% CI, 1.25–2.47).	

Abbreviations: MetSyn Metabolic Syndrome; CI Confidence Interval; COPD Chronic Obstructive Pulmonary Disease; PM Particulate Matter; CVD Cardiovascular disease; HDL High Density Protein; HR Hazards Ratio; OR Odds Ratio; USA United States of America. PM<sub>2.5</sub> Particulate Matter <2.5µm in Aerodynamic Diameter.



**Figure 1.** Schematic of biological mechanisms underlying PM-induced MetSyn, COPD, and CVD. (a) PM-associated Vascular Effects: PM exposure leads to the hypomethylation of TLR4, which may increase systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as *Alu* hypomethylation and autonomic imbalance, which may elevate DBP. Increased SBP and DBP contribute to the development of hypertension, a key feature of MetSyn. (b) PM associated MetSyn Phenotype Development: Inhalation of PM elicits the generation of reactive oxygen species (ROS), ER stress, and elevated cytokine levels, such as TNF- $\alpha$ , and IL-6, which in turn activates signal transduction cascades by inducing the activity of cellular kinases (JNK, PKC, IKK). Kinase activation can directly lead to systemic inflammation or do so indirectly by first activating inflammatory pathways (AP-1, NF- $\kappa$ B). (c) PM-associated Lipid Changes (ATX Autotaxin; LPC lysophosphatidylcholine; PLA phospholipase; PAPC 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine; SAPC 1-stearoyl-2-arachidonoyl-sn-glycero-phosphocholine; oxLDL oxidized LDL; PA phosphatidic acid). (d) Systemic Inflammation contributes to the development of insulin resistance, abdominal obesity, hypertriglyceridemia, and low HDL, all of which are defining characteristics of MetSyn. (e) MetSyn then increases affected individuals' risk of developing COPD and CVD. Lines with no arrowhead ( $\curvearrowright$ ) indicate enzymatic contribution to downstream catabolic reactions.

Furthermore, individuals with preexisting MetSyn are more susceptible to the inflammatory effects of PM exposure [2,32,36]. Chronic exposure to ambient air pollution leads to weight gain secondary to local and systemic inflammation, increasing the risk of developing the etiological components of MetSyn [37,38]. As MetSyn affects more than 30% of adults in the United States, patients with MetSyn represent a large percentage of the population that is especially sensitive to PM [2,32,39,40].

### 3.2. Epidemiology of CVD and PM Exposure

PM exposure has been linked to an increased risk of CVD such as myocardial infarction, ischemic heart disease, stroke, heart failure, arrhythmias, and venous thromboembolism (Figure 1e [41]). Short-term PM exposure was associated with an increased number of hospital admissions for CVD, and both fatal and non-fatal cardiovascular events [34]. Long-term exposure is associated with an even greater increase of cardiovascular disease and mortality, including postmenopausal women from U.S. metropolitan areas (Table 1 [35,41]).

### 3.3. Epidemiology of Chronic Obstructive Pulmonary Disease (COPD) and PM Exposure

PM exposure can elicit the development or exacerbation of COPD (Figure 1e). Black carbon, an indicator of traffic-related fine particulate air pollution, was associated with an increased risk for COPD hospitalization in a population-based study of 467,994 subjects [27]. An increase of 10  $\mu\text{g}/\text{m}^3$  in  $\text{PM}_{2.5}$  nearly doubled the hospital admissions for COPD exacerbations from 1999 to 2002 in a study of Medicare billing claims from 11.5 million enrollees [10]. Similar to individuals with preexisting MetSyn, COPD patients are more susceptible to the harmful effects of PM exposure and often experience acute exacerbations due to bacterial and viral infections contracted in the wake of PM exposure [42,43]. Additionally, long-term PM exposure has been implicated as a potential indicator of increased respiratory mortality among COPD patients [43]. In a 2014 cross-sectional study, it was determined that there was a 2.53% increase in COPD deaths per 10  $\mu\text{g}/\text{m}^3$  increase of  $\text{PM}_{2.5}$  over a six-day period, Table 1 [29].

## 4. Biological Mechanisms Underlying PM-Induced Metabolic and Cardiopulmonary Diseases

### 4.1. Mechanisms of PM Associated MetSyn

Air pollution has been implicated in the pathogenesis of MetSyn by causing systemic inflammation associated with metabolic disorders [25]. This chronic inflammation is characterized by cytokine production, and activation of a network of inflammatory signaling pathways. Adipose tissue is involved in the inflammatory response and mediators [44]. Tumor Necrosis Factor-alpha ( $\text{TNF-}\alpha$ ) is a pro-inflammatory cytokine that is overexpressed in the adipose tissue of obese mice and humans after PM exposure [45,46]. Cytokines such as  $\text{TNF-}\alpha$  and Interleukin-6 (IL-6), lipids, reactive oxygen species (ROS), or endoplasmic reticulum (ER) stress activate various signal transduction cascades by inducing the activity of cellular kinases, namely c-Jun N-terminal Kinase (JNK), I-kappa B kinase (IKK), and Protein Kinase C (PKC) (Figure 1b [36,44]). These kinase phosphorylate serine residues of insulin receptor substrate-1 and -2 in order to block insulin action. JNK and IKK also promote further inflammatory gene expression by activating the two principal inflammatory pathways: activator protein 1 (AP-1) and nuclear factor kappa-B (NF- $\kappa$ B), respectively [44]. Adipocyte hypertrophy in response to fat consumption and accumulation can induce cellular rupture, attracting macrophages to reinforce the inflammatory response. In this context, hypertrophied adipocytes rupture frequently, leading to the deposition of fat in organs other than adipose tissue, Figure 1b [36].

In animal models, air pollution has been linked to hypertension, alterations in blood lipids, insulin resistance, and obesity, all of which contribute to the low-grade systemic inflammation of MetSyn (Figure 1d). Pregnant rats exposed to unfiltered Beijing air for 19 days (starting on gestational day 1), starting on their first day of gestation, were heavier at the end of their pregnancy compared to those who were exposed to filtered air. Additionally, 8-week-old pups who were prenatally and postnatally exposed to unfiltered air were significantly heavier than those who were exposed to filtered air. The PM-exposed pups also demonstrated significantly lower levels of Glucagon-like Peptide 1 (GLP-1), an incretin hormone that enhances insulin secretion and has anti-inflammatory properties within adipose tissue. Both the previously pregnant rats and the 8-week-old pups displayed perivascular and peribronchial inflammation in the lungs. Particulate matter caused PM-exposed rats to experience weight gain secondary to systemic inflammation, increased insulin resistance and lung inflammation,

which are etiological components of MetSyn. This study suggests that chronic exposure to particulate matter increases the risk of developing MetSyn [25]. In a murine model, exposure to PM<sub>10</sub> showed elevated neutrophil concentrations and upregulated TNF- $\alpha$  and IL-6 levels, all of which indicate an inflammatory response. Additionally, mice exposed to PM experienced an upregulation of genes related to inflammation, cholesterol and lipids, Figure 1a [1]. In another murine model, mice that were fed high-fat chow for 10 weeks and exposed to 72.7  $\mu\text{g}/\text{m}^3$  of PM<sub>2.5</sub> for 6 h/day, 5 days/week over 24 weeks experienced exaggerated insulin resistance, systemic inflammation, and visceral adiposity demonstrated by elevated TNF- $\alpha$ , IL-6 and PKC expression, Figure 1b [26,37].

In humans, ambient PM has also been found to induce DNA hypomethylation, which is associated with increases in BP, Figure 1a. Hypomethylation gives rise to vascular smooth muscle proliferation and lipid deposition due to mutations, causing the formation of fibrocellular lesions and subsequent increases in BP [47]. Autonomic imbalance has also been suggested as a possible mechanism through which PM increases diastolic BP, a component of MetSyn, Figure 1a [19,21,48]. Exposure to PM<sub>2.5</sub> lowers repetitive element *Arthrobacter luteus* (*Alu*) methylation, while exposure to PM<sub>2.5–10</sub> lowers toll-like receptor 4 (*TLR4*) methylation. Both *Alu* and *TLR4* hypomethylation are associated with increased diastolic BP, while only *TLR4* hypomethylation is associated with increased systolic BP, Figure 1a [47].

#### 4.2. PM Exposure and COPD

Inflammation and tissue remodeling are key features of airflow obstruction in asthma and obstructive airways disease (OAD), as discussed in two reviews [49,50]. PM exposure leads to the pathogenesis of COPD by inducing pulmonary and systemic inflammation (Figure 1e). Chronic exposure to air pollution can prevent clearance of PM from the lung, resulting in particle accumulation in lung tissues. The accumulation of PM in the respiratory tract induces the production of pro-inflammatory mediators, namely TNF- $\alpha$  and IL-6, by alveolar macrophages and lung epithelial cells (Figure 1b [43]).

Inflammatory cytokines that increase in sputum and bronchoalveolar lavage fluid are also elevated in COPD patients, suggesting inflammatory mediators elicit both a local inflammatory response in the lung tissues and secondary systemic inflammatory response [51]. The inflammatory response is characterized by tissue proliferation in the small airways and tissue destruction in the lung parenchyma, causing subsequent airway obstruction, leading to the development of COPD [43].

#### 4.3. PM Exposure and CVD

Recent studies have associated systemic vascular dysfunction with lung disease (the vascular hypothesis) and prospective studies have demonstrated an association between impaired lung function and central arterial stiffness even before the development of CVD [52–56]. Hallmarks of PM exposure include vascular endothelial dysfunction, systemic inflammation, and subsequent end-organ damage [13,57–63].

In a murine model, the effects of long-term PM exposure on atherosclerosis potentiation, vasomotor tone alteration, and vascular inflammation were evaluated. This study found that PM-exposed and high-fat chow fed mice exhibited significant plaque burden, compared to PM-exposed mice with a normal chow diet [31]. Another murine study demonstrated that acute carbon black exposure led to impaired cardiac function in senescent mice through cardiac changes such as diminished myocardial contractibility, elevated right atrial and pulmonary vascular pressures, and increased pulmonary vascular resistance [30].

In humans, three PM-related pathways have been linked to adverse cardiovascular health effects: (1) the generation of systemic inflammation through the release of circulating pro-inflammatory and pro-oxidative mediators from PM-stimulated lung cells (Figure 1b), (2) alterations in cardiac autonomic function induced by PM interactions with lung receptors (Figure 1a), and (3) the translocation of PM into the bloodstream [33,41,64]. PM inhalation triggers local and systemic inflammation through these

biological mechanisms depending on the size of the PM. Both coarse (PM<sub>10-2.5</sub>) and fine (PM<sub>2.5</sub>) PM can trigger the release of inflammatory mediators that spread to general circulation, where they elicit systemic inflammation [41]. Generation of ROS is also involved in the PM-induced pro-inflammatory pathway as demonstrated by elevated ROS in rat lung and heart after PM exposure (Figure 1b [65]). ROS have been linked to atherosclerosis, vascular dysfunction, cardiac arrhythmias, and myocardial injury [66]. Coarse and fine particles also cause impairment of the autonomic control of the heart, by enhancing sympathetic tone and decreasing heart rate variability (Figure 1a [41,67]). Both decreased heart rate variability, an indicator of poor cardiovascular prognosis, and elevated sympathetic tone predispose individuals to arrhythmia-associated cardiac death [66,67]. Ultrafine particles (PM < 0.1 µm) can translocate into the bloodstream, where they promote events by enhancing platelet aggregation and endothelial cell activation [41]. Furthermore, not only does PM exposure put individuals at risk for the development of CVD, but that MetSyn phenotypes also influence these pathways' differential response to PM exposure.

### 5. MetSyn as a Risk Factor for COPD and CVD

PM-induced systemic inflammation and co-existing MetSyn have been implicated in the development and progression of cardiopulmonary diseases, Figure 1e [33,37,38,60,68,69]. Individuals with MetSyn are predisposed to systemic inflammation, a key feature of COPD [28], and nearly half of COPD patients have coexisting MetSyn [68,70,71]. A cross-sectional study demonstrated that systemic inflammatory markers were elevated in COPD patients with preexisting MetSyn, compared to those without MetSyn [28]. This study suggests that systemic inflammation is more severe in patients with coexisting COPD and MetSyn than in healthy individuals [28,72]. Additionally, systemic inflammation contributes to the development of cardiovascular disease, reaffirming that the concurrence of MetSyn and COPD increases the risk of cardiovascular morbidity and mortality [28].

Individuals with MetSyn are especially susceptible to the cardiovascular effects of air pollution [73]. Exposed individuals with MetSyn experience increased oxidative stress, which is further elevated by aromatic hydrogen and metal nanoparticle components of air pollution. Consequently, an oxidative stress cascade is activated, leading to CVD (Figure 1b,c [38]). In a case-crossover study, MetSyn individuals with no preexisting CVD who were exposed to ambient ultrafine particles experienced PM-induced cardiovascular effects, demonstrated by changes in heart rate variability and cardiac repolarization [32]. Similarly, a population-based study reported that, after PM<sub>2.5</sub> exposure, those with MetSyn exhibited substantial decreases in heart rate variability relative to those without MetSyn; therefore, PM exposure increases cardiovascular risk among MetSyn patients with or without cardiovascular disease [33].

### 6. Cardiopulmonary Effects of WTC-PM-Exposure

Our group has developed leadership in pathophysiologic investigation of WTC-associated disease [16–18]. FDNY rescue/recovery workers exposed to WTC-PM developed respiratory symptoms and were diagnosed with chronic pulmonary diseases, including OAD and airway hyperreactivity [15,39,74–85]. Induced sputum drawn from WTC-exposed FDNY firefighters 10-months post exposure showed elevated levels of PM and evidence of continuing inflammation due to abnormal accumulation of pro-inflammatory cells [84,86]. The WTC-exposed FDNY cohort experienced significant decreases in Forced Expiratory Volume in 1 second (FEV<sub>1</sub>) [51,87].

In addition to the pulmonary effects of WTC exposure, there was an increase in the risk for CVD-related hospitalizations post WTC exposure [88,89]. CVD symptoms such as chest pain were found in 8% of WTC-exposed workers and volunteers between 2002 and 2004 [90]. Furthermore, pulmonary arteriopathy was present in 58% of lung biopsies from a small group of WTC-exposed individuals [91].

Biomarkers of MetSyn, traditionally seen as risk factors for CVD, predict WTC-associated OAD [13,14,92]. Specifically, BMI-adjusted triglycerides, HDL, heart rate, and leptin were significantly

elevated, indicating that metabolic risk factors held key roles in the inflammatory cascade from PM exposure [13]. Also, our study of computed tomography scans of WTC firefighters showed that elevated Pulmonary-Artery-to-Aorta diameters ratio (PA/A) is correlated with future development of FEV<sub>1</sub> [12].

Our investigation of the metabolome of WTC-associated OAD has identified prominent pathways involving lipids in the same exposed firefighters [12]. Pathological imbalances in lipid metabolism are well-defined initiators of systemic inflammation, triglyceridemia, CVD, and OAD. Aspects of our cohort's lipid metabolome that have been correlated with OAD include arachidonic acid, lysophosphatidic acid (LPA), lysolipids, phospholipids, polyunsaturated fatty acids, and phosphatidylcholines (1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine and 1-stearoyl-2-arachidonoyl-sn-glycero-phosphocholine) [12]. Studies have connected these intermediates to a cascade initiated by ROS production, and culminating in triglyceride production and systemic inflammation, Figure 1c [12]. The association of ROS production and lipid imbalance yields a PM-initiated pathway of catabolism, resulting in lipid-mediated inflammation, CVD, and COPD [12].

Our recent work has focused on the receptor for advanced glycation end products (RAGE)/LPA axis [12]. Our collaborators have identified a ligand-receptor interaction between LPA and the advanced glycation end-product receptor (RAGE), a cytoplasmic IgG receptor localized to alveolar macrophages, alveolar endothelium, and smooth muscle within lung tissue [12]. Specifically, we have shown that elevated soluble RAGE and LPA are associated with WTC-LI in firefighters exposed to WTC-PM and mice deficient in RAGE are protected from the adverse pulmonary effects [12].

## 7. Conclusions and Future Investigations

Overall, we found that exposure to particulate matter elicits pulmonary and systemic inflammation. Systemic inflammation leads to the development of MetSyn and cardiopulmonary disease, such as COPD and CVD. Individuals with these preexisting conditions are more susceptible to the inflammatory effects of PM exposure, which can further exacerbate their conditions. Additionally, MetSyn predisposes individuals to PM-induced pathogenesis of COPD and CVD; therefore, further research is required to discover and elucidate therapeutic targets of these comorbidities.

**Author Contributions:** All authors made substantial contributions to the study. All authors participated in study conception and design, data analysis and interpretation, and manuscript preparation. Primary investigator A.N.; Study design E.A.C., G.C., and A.N.; Statistical Analysis Not Applicable; Data interpretation E.A.C., G.C., and A.N. All authors participated in writing and revision of the report and approval of the final version. Conceptualization, A.N. and E.A.C.; Methodology, E.A.C. and A.N.; Software, E.A.C. and G.C.; Validation, E.A.C., A.N., and S.K.; Formal Analysis, E.A.C., A.N. and G.C.; Resources, A.N.; Data Curation, E.A.C., A.N., A.T., D.O., and J.S.K.; Writing – Original Draft Preparation, ALL AUTHORS; Writing – Review & Editing, ALL AUTHORS; Visualization, E.A.C., A.T., J.S.K., G.C., D.O., and A.N.; Supervision, Administration and Funding Acquisition, A.N.

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## References

1. Brocato, J.; Sun, H.; Shamy, M.; Kluz, T.; Alghamdi, M.A.; Khoder, M.I.; Chen, L.C.; Costa, M. Particulate matter from Saudi Arabia induces genes involved in inflammation, metabolic syndrome and atherosclerosis. *J. Toxicol. Environ. Health A* **2014**, *77*, 751–766. [CrossRef]
2. Chen, J.C.; Schwartz, J. Metabolic syndrome and inflammatory responses to long-term particulate air pollutants. *Environ. Health Persp.* **2008**, *116*, 612–617. [CrossRef]
3. World Health Organization. 9 Out of 10 People Worldwide Breathe Polluted Air, But More Countries Are Taking Action. 2 May 2018. Available online: <https://www.who.int/news-room/detail/02-05-2018-9-out-of-10-people-worldwide-breathe-polluted-air-but-more-countries-are-taking-action> (accessed on 29 January 2019).



4. Peters, A.; Dockery, D.W.; Muller, J.E.; Mittleman, M.A. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation* **2001**, *103*, 2810–2815. [[CrossRef](#)]
5. Peters, A.; von Klot, S.; Heier, M.; Trentinaglia, I.; Hormann, A.; Wichmann, H.E.; Lowel, H. Exposure to traffic and the onset of myocardial infarction. *New Engl J. Med.* **2004**, *351*, 1721–1730. [[CrossRef](#)]
6. Wellenius, G.A.; Schwartz, J.; Mittleman, M.A. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke* **2005**, *36*, 2549–2553. [[CrossRef](#)]
7. Wellenius, G.A.; Yeh, G.Y.; Coull, B.A.; Suh, H.H.; Phillips, R.S.; Mittleman, M.A. Effects of ambient air pollution on functional status in patients with chronic congestive heart failure: A repeated-measures study. *Environ. Health* **2007**, *6*, 26. [[CrossRef](#)]
8. Wellenius, G.A.; Coull, B.A.; Batalha, J.R.; Diaz, E.A.; Lawrence, J.; Godleski, J.J. Effects of ambient particles and carbon monoxide on supraventricular arrhythmias in a rat model of myocardial infarction. *Inhal. Toxicol.* **2006**, *18*, 1077–1082. [[CrossRef](#)]
9. Wellenius, G.A.; Schwartz, J.; Mittleman, M.A. Particulate air pollution and hospital admissions for congestive heart failure in seven united states cities. *Am. J. Cardiol.* **2006**, *97*, 404–408. [[CrossRef](#)]
10. Dominici, F.; Peng, R.D.; Bell, M.L.; Pham, L.; McDermott, A.; Zeger, S.L.; Samet, J.M. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* **2006**, *295*, 1127–1134. [[CrossRef](#)]
11. Simkhovich, B.Z.; Kleinman, M.T.; Kloner, R.A. Particulate air pollution and coronary heart disease. *Curr. Opin. Cardiol.* **2009**, *24*, 604–609. [[CrossRef](#)]
12. Crowley, G.; Kwon, S.; Haider, S.H.; Caraher, E.J.; Lam, R.; St-Jules, D.E.; Liu, M.; Prezant, D.J.; Nolan, A. Metabolomics of world trade center-lung injury: A machine learning approach. *BMJ Open Respir. Res.* **2018**, *5*, e000274. [[CrossRef](#)]
13. Naveed, B.; Weiden, M.D.; Kwon, S.; Gracely, E.J.; Comfort, A.L.; Ferrier, N.; Kasturiarachchi, K.J.; Cohen, H.W.; Aldrich, T.K.; Rom, W.N.; et al. Metabolic syndrome biomarkers predict lung function impairment: A nested case-control study. *Am. J. Respir. Crit. Care Med.* **2012**, *185*, 392–399. [[CrossRef](#)]
14. Tsukiji, J.; Cho, S.J.; Echevarria, G.C.; Kwon, S.; Joseph, P.; Schenck, E.J.; Naveed, B.; Prezant, D.J.; Rom, W.N.; Schmidt, A.M.; et al. Lysophosphatidic acid and apolipoprotein a1 predict increased risk of developing world trade center-lung injury: A nested case-control study. *Biomarkers* **2014**, *19*, 159–165. [[CrossRef](#)]
15. Weiden, M.D.; Kwon, S.; Caraher, E.; Berger, K.I.; Reibman, J.; Rom, W.N.; Prezant, D.J.; Nolan, A. Biomarkers of world trade center particulate matter exposure: Physiology of distal airway and blood biomarkers that predict FEV(1) decline. In *Seminars in respiratory and critical care medicine*; NIH Public Access: Bethesda, MD, USA, 2015; Volume 36, p. 323.
16. Holguin, F. The metabolic syndrome as a risk factor for lung function decline. *Am. J. Respir. Crit. Care Med.* **2012**, *185*, 352–353. [[CrossRef](#)]
17. Balmes, J.R. Can we predict who will develop chronic sequelae of acute inhalational injury? *Chest* **2012**, *142*, 278–279. [[CrossRef](#)]
18. Antao, V.C. The world trade center disaster: A tragic source of medical advancement. *Eur. Respir. J.* **2013**, *41*, 999–1001. [[CrossRef](#)]
19. Grundy, S.M.; Cleeman, J.I.; Daniels, S.R.; Donato, K.A.; Eckel, R.H.; Franklin, B.A.; Gordon, D.J.; Krauss, R.M.; Savage, P.J.; Smith, S.C., Jr.; et al. Diagnosis and management of the metabolic syndrome: An american heart association/national heart, lung, and blood institute scientific statement. *Circulation* **2005**, *112*, 2735–2752. [[CrossRef](#)]
20. Huang, W.; Wang, L.; Li, J.; Liu, M.; Xu, H.; Liu, S.; Chen, J.; Zhang, Y.; Morishita, M.; Bard, R.L.; et al. Short-term blood pressure responses to ambient fine particulate matter exposures at the extremes of global air pollution concentrations. *Am. J. Hypertens.* **2018**, *31*, 590–599.
21. Brook, R.D.; Rajagopalan, S. Particulate matter, air pollution, and blood pressure. *J. Am. Soc. Hypertens.* **2009**, *3*, 332–350. [[CrossRef](#)]
22. Chobanian, A.V.; Bakris, G.L.; Black, H.R.; Cushman, W.C.; Green, L.A.; Izzo Jr, J.L.; Jones, D.W.; Materson, B.J.; Oparil, S.; Wright Jr, J.T.; et al. National Heart, Institute Blood, and Committee National High Blood Pressure Education Program Coordinating. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* **2003**, *42*, 1206–1252. [[CrossRef](#)]
23. Tenenbaum, A.; Fisman, E.Z.; Motro, M. Metabolic syndrome and type 2 diabetes mellitus: Focus on peroxisome proliferator activated receptors (PPAR). *Cardiovasc. Diabetol.* **2003**, *2*, 4. [[CrossRef](#)]

24. Bowe, B.; Xie, Y.; Li, T.; Yan, Y.; Xian, H.; Al-Aly, Z. The 2016 global and national burden of diabetes mellitus attributable to PM<sub>2.5</sub> air pollution. *Lancet Planet. Health* **2018**, *2*, e301–e312. [[CrossRef](#)]
25. Wei, Y.; Zhang, J.J.; Li, Z.; Gow, A.; Chung, K.F.; Hu, M.; Sun, Z.; Zeng, L.; Zhu, T.; Jia, G.; et al. Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: Findings from a natural experiment in Beijing. *FASEB J.* **2016**, *30*, 2115–2122. [[CrossRef](#)]
26. Sun, Q.; Yue, P.; Deilulis, J.A.; Lumeng, C.N.; Kampfrath, T.; Mikolaj, M.B.; Cai, Y.; Ostrowski, M.C.; Lu, B.; Parthasarathy, S.; et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation* **2009**, *119*, 538–546. [[CrossRef](#)]
27. Gan, W.Q.; FitzGerald, J.M.; Carlsten, C.; Sadatsafavi, M.; Brauer, M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. *Am. J. Respir. Crit. Care Med.* **2013**, *187*, 721–727. [[CrossRef](#)]
28. Vujic, T.; Nagorni, O.; Maric, G.; Popovic, L.; Jankovic, J. Metabolic syndrome in patients with chronic obstructive pulmonary disease: Frequency and relationship with systemic inflammation. *Hippokratia* **2016**, *20*, 110–114.
29. Samoli, E.; Stafoggia, M.; Rodopoulou, S.; Ostro, B.; Alessandrini, E.; Basagana, X.; Diaz, J.; Faustini, A.; Gandini, M.; Karanasiou, A.; et al. Which specific causes of death are associated with short term exposure to fine and coarse particles in southern Europe? Results from the med-particles project. *Environ. Int.* **2014**, *67*, 54–61. [[CrossRef](#)]
30. Tankersley, C.G.; Champion, H.C.; Takimoto, E.; Gabrielson, K.; Bedja, D.; Misra, V.; El-Haddad, H.; Rabold, R.; Mitzner, W. Exposure to inhaled particulate matter impairs cardiac function in senescent mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2008**, *295*, R252–R263. [[CrossRef](#)]
31. Sun, Q.; Wang, A.; Jin, X.; Natanzon, A.; Duquaine, D.; Brook, R.D.; Aguinaldo, J.G.; Fayad, Z.A.; Fuster, V.; Lippmann, M.; et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA* **2005**, *294*, 3003–3010. [[CrossRef](#)]
32. Devlin, R.B.; Smith, C.B.; Schmitt, M.T.; Rappold, A.G.; Hinderliter, A.; Graff, D.; Carraway, M.S. Controlled exposure of humans with metabolic syndrome to concentrated ultrafine ambient particulate matter causes cardiovascular effects. *Toxicol. Sci.* **2014**, *140*, 61–72. [[CrossRef](#)]
33. Park, S.K.; Auchincloss, A.H.; O’Neill, M.S.; Prineas, R.; Correa, J.C.; Keeler, J.; Barr, R.G.; Kaufman, J.D.; Diez Roux, A.V. Particulate air pollution, metabolic syndrome, and heart rate variability: The multi-ethnic study of atherosclerosis (MESA). *Environ. Health Perspect.* **2010**, *118*, 1406–1411. [[CrossRef](#)]
34. Chang, C.C.; Chen, P.S.; Yang, C.Y. Short-term effects of fine particulate air pollution on hospital admissions for cardiovascular diseases: A case-crossover study in a tropical city. *J. Toxicol. Environ. Health Part A* **2015**, *78*, 267–277. [[CrossRef](#)]
35. Miller, K.A.; Siscovick, D.S.; Sheppard, L.; Shepherd, K.; Sullivan, J.H.; Anderson, G.L.; Kaufman, J.D. Long-term exposure to air pollution and incidence of cardiovascular events in women. *New Eng. J. Med.* **2007**, *356*, 447–458. [[CrossRef](#)]
36. Monteiro, R.; Azevedo, I. Chronic inflammation in obesity and the metabolic syndrome. *Mediat. Inflamm.* **2010**, *2010*. [[CrossRef](#)]
37. Brook, R.D.; Rajagopalan, S.; Pope, C.A., 3rd; Brook, J.R.; Bhatnagar, A.; Diez-Roux, A.V.; Holguin, F.; Hong, Y.; Luepker, R.V.; Mittleman, M.A.; et al. Kaufman, Epidemiology American Heart Association Council on, Council on the Kidney in Cardiovascular Disease Prevention, Physical Activity Council on Nutrition, and Metabolism. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* **2010**, *121*, 2331–2378.
38. Hutcheson, R.; Rocic, P. The metabolic syndrome, oxidative stress, environment, and cardiovascular disease: The great exploration. *Exp. Diabetes Res.* **2012**, *2012*. [[CrossRef](#)]
39. Webber, M.P.; Lee, R.; Soo, J.; Gustave, J.; Hall, C.B.; Kelly, K.; Prezant, D. Prevalence and incidence of high risk for obstructive sleep apnea in world trade center-exposed rescue/recovery workers. *Sleep Breath.* **2011**, *15*, 283–294. [[CrossRef](#)]
40. Moore, J.X.; Chaudhary, N.; Akinyemiju, T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, national health and nutrition examination survey, 1988–2012. *Prev. Chronic. Dis.* **2017**, *14*, E24. [[CrossRef](#)]
41. Martinelli, N.; Olivieri, O.; Girelli, D. Air particulate matter and cardiovascular disease: A narrative review. *Eur. J. Intern. Med.* **2013**, *24*, 295–302. [[CrossRef](#)]

42. Sint, T.; Donohue, J.F.; Ghio, A.J. Ambient air pollution particles and the acute exacerbation of chronic obstructive pulmonary disease. *Inhal. Toxicol.* **2008**, *20*, 25–29. [[CrossRef](#)]
43. Ling, S.H.; van Eeden, S.F. Particulate matter air pollution exposure: Role in the development and exacerbation of chronic obstructive pulmonary disease. *Int. J. Chronic Obstr. Pulmon. Dis.* **2009**, *4*, 233–243. [[CrossRef](#)]
44. Hotamisligil, G.S. Inflammation and metabolic disorders. *Nature* **2006**, *444*, 860–867. [[CrossRef](#)]
45. Tsai, D.H.; Amyai, N.; Marques-Vidal, P.; Wang, J.L.; Riediker, M.; Mooser, V.; Paccaud, F.; Waeber, G.; Vollenweider, P.; Bochud, M. Effects of particulate matter on inflammatory markers in the general adult population. *Part. Fibre Toxicol.* **2012**, *9*, 24. [[CrossRef](#)]
46. Xu, X.; Yavar, Z.; Verdin, M.; Ying, Z.; Mihai, G.; Kampfrath, T.; Wang, A.; Zhong, M.; Lippmann, M.; Chen, L.C.; et al. Effect of early particulate air pollution exposure on obesity in mice: Role of p47phox. *Arterioscler. Thromb. Vas. Biol.* **2010**, *30*, 2518–2527. [[CrossRef](#)]
47. Bellavia, A.; Urch, B.; Speck, M.; Brook, R.D.; Scott, J.A.; Albeti, B.; Behbod, B.; North, M.; Valeri, L.; Bertazzi, P.A.; et al. DNA hypomethylation, ambient particulate matter, and increased blood pressure: Findings from controlled human exposure experiments. *J. Am. Heart Assoc.* **2013**, *2*, e000212. [[CrossRef](#)]
48. Urch, B.; Silverman, F.; Corey, P.; Brook, J.R.; Lukic, K.Z.; Rajagopalan, S.; Brook, R.D. Acute blood pressure responses in healthy adults during controlled air pollution exposures. *Environ. Health Perspect.* **2005**, *113*, 1052–1055. [[CrossRef](#)]
49. Cosio, M.G.; Saetta, M.; Agusti, A. Immunologic aspects of chronic obstructive pulmonary disease. *New Engl. J. Med.* **2009**, *360*, 2445–2454. [[CrossRef](#)]
50. Davies, D.E.; Wicks, J.; Powell, R.M.; Puddicombe, S.M.; Holgate, S.T. Airway remodeling in asthma: New insights. *J. Allergy Clin. Immunol.* **2003**, *111*, 215–225.
51. Barnes, P.J. Chronic obstructive pulmonary disease: Effects beyond the lungs. *PLoS Med.* **2010**, *7*, e1000220. [[CrossRef](#)]
52. Zureik, M.; Benetos, A.; Neukirch, C.; Courbon, D.; Bean, K.; Thomas, F.; Ducimetiere, P. Reduced pulmonary function is associated with central arterial stiffness in men. *Am. J. Respir. Crit. Care Med.* **2001**, *164*, 2181–2185. [[CrossRef](#)]
53. Tockman, M.S.; Pearson, J.D.; Fleg, J.L.; Metter, E.J.; Kao, S.Y.; Rampal, K.G.; Cruise, L.J.; Fozard, J.L. Rapid decline in FEV1. A new risk factor for coronary heart disease mortality. *Am. J. Respir. Crit. Care Med.* **1995**, *151*, 390–398. [[CrossRef](#)]
54. Mannino, D.M.; Thorn, D.; Swensen, A.; Holguin, F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in chronic obstructive pulmonary disease. *Eur. Respir. J.* **2008**, *32*, 962–969. [[CrossRef](#)]
55. Taraseviciene-Stewart, L.; Scerbavicius, R.; Choe, K.H.; Moore, M.; Sullivan, A.; Nicolls, M.R.; Fontenot, A.P.; Tuder, R.M.; Voelkel, N.F. An animal model of autoimmune emphysema. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 734–742.
56. Voelkel, N.; Taraseviciene-Stewart, L. Emphysema: An autoimmune vascular disease? *PATS* **2005**, *2*, 23–25. [[CrossRef](#)]
57. Mills, N.L.; Tornqvist, H.; Gonzalez, M.C.; Vink, E.; Robinson, S.D.; Soderberg, S.; Boon, N.A.; Donaldson, K.; Sandstrom, T.; Blomberg, A.; et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *New Engl. J. Med.* **2007**, *357*, 1075–1082. [[CrossRef](#)]
58. Tornqvist, H.; Mills, N.L.; Gonzalez, M.; Miller, M.R.; Robinson, S.D.; Megson, I.L.; Macnee, W.; Donaldson, K.; Soderberg, S.; Newby, D.E.; et al. Persistent endothelial dysfunction in humans after diesel exhaust inhalation. *Am. J. Respir. Crit. Care Med.* **2007**, *176*, 395–400. [[CrossRef](#)]
59. Broekhuizen, R.; Wouters, E.F.; Creutzberg, E.C.; Schols, A.M. Raised CRP levels mark metabolic and functional impairment in advanced copd. *Thorax* **2006**, *61*, 17–22. [[CrossRef](#)]
60. Gan, W.Q.; Man, S.F.; Senthilselvan, A.; Sin, D.D. Association between chronic obstructive pulmonary disease and systemic inflammation: A systematic review and a meta-analysis. *Thorax* **2004**, *59*, 574–580. [[CrossRef](#)]
61. Koenig, W. Inflammation and coronary heart disease: An overview. *Cardiol. Rev.* **2001**, *9*, 31–35. [[CrossRef](#)]
62. Hoffmeister, A.; Rothenbacher, D.; Bazner, U.; Frohlich, M.; Brenner, H.; Hombach, V.; Koenig, W. Role of novel markers of inflammation in patients with stable coronary heart disease. *Am. J. Cardiol.* **2001**, *87*, 262–266. [[CrossRef](#)]

63. Sin, D.D.; Man, S.F. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* **2003**, *107*, 1514–1519. [[CrossRef](#)]
64. Brook, R.D. Cardiovascular effects of air pollution. *Clin. Sci.* **2008**, *115*, 175–187. [[CrossRef](#)]
65. Gurgueira, S.A.; Lawrence, J.; Coull, B.; Murthy, G.G.; Gonzalez-Flecha, B. Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. *Environ. Health Perspect.* **2002**, *110*, 749–755. [[CrossRef](#)]
66. Du, Y.; Xu, X.; Chu, M.; Guo, Y.; Wang, J. Air particulate matter and cardiovascular disease: The epidemiological, biomedical and clinical evidence. *J. Thorac. Dis.* **2016**, *8*, E8–E19.
67. Franchini, M.; Mannucci, P.M. Thrombogenicity and cardiovascular effects of ambient air pollution. *Blood* **2011**, *118*, 2405–2412. [[CrossRef](#)]
68. Watz, H.; Waschki, B.; Kirsten, A.; Muller, K.C.; Kretschmar, G.; Meyer, T.; Holz, O.; Magnussen, H. The metabolic syndrome in patients with chronic bronchitis and copd: Frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* **2009**, *136*, 1039–1046. [[CrossRef](#)]
69. Zheng, Y.; Stein, R.; Kwan, T.; Yu, C.; Kwan, J.; Chen, S.L.; Hu, D. Evolving cardiovascular disease prevalence, mortality, risk factors, and the metabolic syndrome in china. *Clin. Cardiol.* **2009**, *32*, 491–497. [[CrossRef](#)]
70. Liu, J.; Wang, H.; Zuo, Y.; Farmer, S.R. Functional interaction between peroxisome proliferator-activated receptor gamma and beta-catenin. *Mol. Cell. Biol.* **2006**, *26*, 5827–5837. [[CrossRef](#)]
71. Ford, E.S.; Giles, W.H.; Dietz, W.H. Prevalence of the metabolic syndrome among us adults: Findings from the third national health and nutrition examination survey. *JAMA* **2002**, *287*, 356–359. [[CrossRef](#)]
72. Hunninghake, D.B. Cardiovascular disease in chronic obstructive pulmonary disease. *PATS* **2005**, *2*, 44–49. [[CrossRef](#)]
73. Pope, C.A., 3rd; Turner, M.C.; Burnett, R.T.; Jerrett, M.; Gapstur, S.M.; Diver, W.R.; Krewski, D.; Brook, R.D. Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality. *Circ. Res.* **2015**, *116*, 108–115.
74. Friedman, S.M.; Maslow, C.B.; Reibman, J.; Pillai, P.S.; Goldring, R.M.; Farfel, M.R.; Stellman, S.D.; Berger, K.I. Case-control study of lung function in world trade center health registry area residents and workers. *Am. J. Respir. Crit. Care Med.* **2011**, *184*, 582–589. [[CrossRef](#)]
75. Banauch, G.I.; Hall, C.; Weiden, M.; Cohen, H.W.; Aldrich, T.K.; Christodoulou, V.; Arcentales, N.; Kelly, K.J.; Prezant, D.J. Pulmonary function after exposure to the world trade center collapse in the new york city fire department. *Am. J. Respir. Crit. Care Med.* **2006**, *174*, 312–319.
76. Prezant, D.J.; Weiden, M.; Banauch, G.I.; McGuinness, G.; Rom, W.N.; Aldrich, T.K.; Kelly, K.J. Cough and bronchial responsiveness in firefighters at the world trade center site. *New Engl. J. Med.* **2002**, *347*, 806–815.
77. Aldrich, T.K.; Gustave, J.; Hall, C.B.; Cohen, H.W.; Webber, M.P.; Zeig-Owens, R.; Cosenza, K.; Christodoulou, V.; Glass, L.; Al-Othman, F.; et al. Lung function in rescue workers at the world trade center after 7 years. *New Engl. J. Med.* **2010**, *362*, 1263–1272. [[CrossRef](#)]
78. Zeig-Owens, R.; Webber, M.P.; Hall, C.B.; Schwartz, T.; Jaber, N.; Weakley, J.; Rohan, T.E.; Cohen, H.W.; Derman, O.; Aldrich, T.K.; et al. Early assessment of cancer outcomes in New York city firefighters after the 9/11 attacks: An observational cohort study. *Lancet* **2011**, *378*, 898–905. [[CrossRef](#)]
79. Webber, M.P.; Gustave, J.; Lee, R.; Niles, J.K.; Kelly, K.; Cohen, H.W.; Prezant, D.J. Trends in respiratory symptoms of firefighters exposed to the world trade center disaster: 2001–2005. *Environ. Health Perspect.* **2009**, *117*, 975–980.
80. Webber, M.P.; Glaser, M.S.; Weakley, J.; Soo, J.; Ye, F.; Zeig-Owens, R.; Weiden, M.D.; Nolan, A.; Aldrich, T.K.; Kelly, K.; et al. Physician-diagnosed respiratory conditions and mental health symptoms seven to nine years following the world trade center disaster. *Am. J. Ind. Med.* **2011**, *54*, 661–671. [[CrossRef](#)]
81. Weakley, J.; Webber, M.P.; Gustave, J.; Kelly, K.; Cohen, H.W.; Hall, C.B.; Prezant, D.J. Trends in respiratory diagnoses and symptoms of firefighters exposed to the world trade center disaster: 2005–2010. *Prev. Med.* **2011**, *53*, 364–369.
82. Weiden, M.D.; Naveed, B.; Kwon, S.; Jung Cho, S.; Comfort, A.L.; Prezant, D.J.; Rom, W.N.; Nolan, A. Cardiovascular disease biomarkers predict susceptibility or resistance to lung injury in world trade center dust exposed firefighters. *Eur. Respir. J.* **2012**, 1023–1030.

83. Soo, J.; Webber, M.P.; Gustave, J.; Lee, R.; Hall, C.B.; Cohen, H.W.; Kelly, K.J.; Prezant, D.J. Trends in probable PTSD in firefighters exposed to the world trade center disaster, 2001–2010. *Disaster Med. Public Health* **2011**, *5* (Suppl. 2), S197–S203. [[CrossRef](#)]
84. Rom, W.N.; Reibman, J.; Rogers, L.; Weiden, M.D.; Oppenheimer, B.; Berger, K.; Goldring, R.; Harrison, D.; Prezant, D. Emerging exposures and respiratory health: World trade center dust. *PATS* **2010**, *7*, 142–145. [[CrossRef](#)]
85. Banauch, G.I.; Alleyne, D.; Sanchez, R.; Olender, K.; Cohen, H.W.; Weiden, M.; Kelly, K.J.; Prezant, D.J. Persistent hyperreactivity and reactive airway dysfunction in firefighters at the world trade center. *Am. J. Respir. Crit. Care Med.* **2003**, *168*, 54–62. [[CrossRef](#)]
86. Fireman, E.M.; Lerman, Y.; Ganor, E.; Greif, J.; Fireman-Shoresh, S.; Liroy, P.J.; Banauch, G.I.; Weiden, M.; Kelly, K.J.; Prezant, D.J. Induced sputum assessment in new york city firefighters exposed to world trade center dust. *Environ. Health Perspect.* **2004**, *112*, 1564–1569. [[CrossRef](#)]
87. Banauch, G.; Weiden, N.; Hall, C.; Cohen, H.W.; Aldrich, T.K.; Arcentales, N.; Kelly, K.J.; Prezant, D.J. Accelerated pulmonary function decline after world trade center particulate exposure in the new york city fire department workforce. *Chest* **2005**, *128*, 213S. [[CrossRef](#)]
88. Jordan, H.T.; Stellman, S.D.; Morabia, A.; Miller-Archie, S.A.; Alper, H.; Laskaris, Z.; Brackbill, R.M.; Cone, J.E. Cardiovascular disease hospitalizations in relation to exposure to the september 11, 2001 world trade center disaster and posttraumatic stress disorder. *J. Am. Heart Assoc.* **2013**, *2*, e000431. [[CrossRef](#)]
89. Lin, S.; Gomez, M.I.; Gensburg, L.; Liu, W.; Hwang, S.A. Respiratory and cardiovascular hospitalizations after the world trade center disaster. *Arch. Environ. Occup. Health* **2010**, *65*, 12–20. [[CrossRef](#)]
90. Perritt, K.R.; Herbert, R.; Levin, S.M.; Moline, J. Work-related injuries and illnesses reported by world trade center response workers and volunteers. *Prehosp. Disaster Med.* **2011**, *26*, 401–407. [[CrossRef](#)]
91. Caplan-Shaw, C.E.; Yee, H.; Rogers, L.; Abraham, J.L.; Parsia, S.S.; Naidich, D.P.; Borczuk, A.; Moreira, A.; Shiau, M.C.; Ko, J.P.; et al. Lung pathologic findings in a local residential and working community exposed to world trade center dust, gas, and fumes. *J. Occup. Environ. Med.* **2011**, *53*, 981–991. [[CrossRef](#)]
92. Nolan, A.; Naveed, B.; Comfort, A.L.; Ferrier, N.; Hall, C.B.; Kwon, S.; Kasturiarachchi, K.J.; Cohen, H.W.; Zeig-Owens, R.; Glaser, M.S.; et al. Inflammatory biomarkers predict airflow obstruction after exposure to world trade center dust. *Chest* **2012**, *142*, 412–418. [[CrossRef](#)]



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