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Review article

Health effects following exposure to dust from the World Trade Center disaster: An update☆

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ABSTRACT

Exposure to dust, smoke, and fumes containing volatile chemicals and particulate matter (PM) from the World Trade Center (WTC) towers' collapse impacted thousands of citizens and first responders (FR; firefighters, medicals staff, police officers) of New York City. Surviving FR and recovery workers are increasingly prone to age-related diseases that their prior WTC dust exposures might expedite or make worse. This review provides an overview of published WTC studies concerning FR/recovery workers' exposure and causal mechanisms of age-related disease susceptibility, specifically those involving the cardiopulmonary and neurological systems. This review also highlights the recent findings of the major health effects of cardiovascular, pulmonary, and neurological health sequelae from WTC dust exposure. To better treat those that risked their lives during and after the disaster of September 11, 2001, the deleterious mechanisms that WTC dust exposure exerted and continue to exert on the heart, lungs, and brain of FR must be better understood.

1. Introduction

Exposure to dust, smoke, and fumes containing volatile chemicals and particulate matter (PM) from the World Trade Center (WTC) towers' collapse immediately impacted thousands of citizens of New York City. Nevertheless, the pervasive nature of effects from these exposures continue to linger. First responders (FR; firefighters, medical staff, police officers) and other recovery workers were exposed to very high concentrations of Ground Zero dust and smoke in the days immediately following the 9/11 disaster. During the first week, PM at several hundred $\mu g/m^3$ was present in the air, with the majority of the particles of diameters >10 μm, and a large component being supercoarse (> 50 μm) [1]. This unique dust was quite alkaline (pH 11–12) and contained cement remnants, glass, asbestos, and a large amount of toxic metals and organics, including polycyclic aromatic hydrocarbons [1,2].

WTC dust was not only encountered by FR/recovery workers, but eventually by clean-up workers, office workers, and residents working or living near Ground Zero. These latter groups were exposed as a result of the dusts having dispersed over a large area (≈1.5 miles diameter) and entering many apartments/offices through damaged windows or still-operating air ventilation systems [1]. However, unlike the dusts faced by the FR/recovery workers, dust encountered by residents and workers were potentially physically different, i.e., if windows were intact, smaller diameter particles entered building air-intake systems and were deposited on/in furniture, carpets, windows, etc. [1].

When one refers to WTC dusts in the period after September 11–13, 2001, this is more of a mixture of the original 9/11 dusts along with pollutants released in diesel exhaust and from cutting torches used to break down metal beams, as well as toxicants released into the air from the ongoing fires burning on/within the Main Pile at Ground Zero ([1,3]). For the purpose of this update, the term "WTC dust" refers specifically to the dusts inhaled by FR and recovery workers, and subsequently by residents/clean-up workers in whose apartments/offices the dusts initially settled and remained undisturbed until they returned.

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Table 1
Consequences of WTC dust exposure in the pulmonary, cardiovascular, and nervous systems.

Design/year	Patient/experimental population information	Findings
Pulmonary system		
Longitudinal cohort study [19]	$N = 10{,}641$	In prospective cohort, 65% were never-smokers. 19.5% of never smokers had $FEV_1 > 64$ ml/yr. FEV_1 change differed significantly by smoking status ($p < 0.001$). 32% of smokers experienced greater-than-expected age-related decline compared to never-smokers.
Longitudinal cohort study [26]	$N = 8969$	Following WTC dust exposure, diagnosis of OAD significantly increased the risk for subsequent chronic rhinosinusitis (RR: 4.24; 95% CI: 3.78–4.76) and GERD (RR: 3.21; 95% CI: 2.93–3.52) diagnoses.
Longitudinal cohort study [63]	$N = 19{,}300$	There were 73 self-reported physician-diagnosed pulmonary fibrosis cases, with a PF incidence rate of 36.7/100,000 person-years. The adjusted hazard ratio (AHR) of PF was higher in those with a medium (AHR = 2.5, 95% CI = 1.1–5.8) and very high level of exposure (AHR = 4.5, 95% CI = 2.0–10.4), compared to those with low exposure.
Longitudinal cohort study [23]	$N = 2137$	A bronchodilator pulmonary function test diagnosed asthma/COPD overlap in 99 subjects (4.6%).
[18]	N/A	Review of WTC biomarker literature found cytokines expressed in stored serum from the first 6 mo after 9/11 attacks can identify individuals at risk for adverse pulmonary function. Biomarkers include AAT, IgE, and eosinophils.
Case/control study [21]	$N = 30$	Assessment of metabolites may allow for identification of biologically relevant therapeutic targets of particulate-associated lung disease. Biomarkers of metabolic syndrome, vascular injury, and inflammation predict development of WTC-related lung injury.
Longitudinal cohort study [17]	$N = 8530$	Prolonged treatment with ICS/LABA (>2 years) was associated with smaller FEV_1 compared to shorter duration treatments (OR 2.36, 95% CI: 2.10–2.67 vs OR 1.52, 95% CI: 1.52–1.77).
Cohort study [64]	$N = 4974$	Lay volunteers compared to affiliated volunteers had greater odds of asthma/RADS (OR_{adj} 1.8; 95% CI:1.2–2.7) and new or worsening lower respiratory symptoms (OR_{adj} 2.0; 95% CI 1.8–2.4).
Cardiovascular system		
Interventional murine study [33]	N = 3–8	Cardiovascular physiology altered 24 h and 1 mo post-dust exposure. Pulmonary artery (PA) mean and peak flow velocity, PA acceleration time, pulmonary acceleration to ejection ratio, aortic acceleration time, left ventricular cardiac output and stroke volume were decreased. PA mean pressure, right ventricular wall thickness, and aortic collagen deposition increased.
Longitudinal cohort study ([10])	$N = 9796$	In total, 489 primary cardiovascular events occurred in FDNY members resulting from exposure to WTC dust. The HR for the primary CVD outcome was 1.44 (95% CI, 1.09–1.90) for the earliest arrival group compared with those who arrived later. Similarly, those who worked at the WTC site for 6 or more months vs those who worked less time at the site were more likely to have a CVD event (HR, 1.30; 95% CI, 1.05–1.60).
Longitudinal cohort study [32]	$N = 6481$	PTSD prevalence was much higher in the cohort (males = 19.9%, females = 25.9%) compared to the general population. Stroke had an increased risk of occurrence in PTSD sufferers with (HR of 2.22; 95% CI, 1.30–3.82) as well as myocardial infarction (HR of 2.51; 95% CI, 1.39–4.57).
Prospective cohort study [40]	$N = 402$	Serum perfluoroalkyl substances were associated with early markers of atherosclerosis and CVD, such as triglycerides, total cholesterol, and LDL cholesterol, in adolescents exposed to the WTC disaster.
[20]	N/A	Particulate matter exposure, such as occurred from the WTC disaster, has shown a connection to metabolic syndrome, cardiovascular pathologic markers, and subsequent development of CVD.
Longitudinal cohort study [30]	$N = 39{,}324$	In women, intense dust cloud exposure was significantly associated with HD (AHR 1.28, 95% CI 1.02–1.61). Participants with PTSD at enrollment had an elevated HD risk (AHR 1.68, 95% CI 1.33–2.12 in women, AHR 1.62, 95% CI 1.34–1.96 in men).
Nervous system		
Prospective cohort study [48,49]	$N = 1193$	FR were at greater risk of cognitive dysfunction compared to age-matched normative data (d = 0.38–0.44). Also, PTSD was associated with moderately-increased risk of cognitive dysfunction (RR = 2.64; 95% CI, 1.95–3.57). There was also an association between time working on-site and lower cognitive functioning (RR = 1.36; 95% CI, 1.03–1.80).
Cross-sectional pilot study [55]	$N = 34$	PTSD may be associated with biomarkers and perhaps parenchymal brain changes related or identical to those observed in AD. PTSD symptom severity was associated with higher A 42/A 40 ratios ($r = 0.36$, $p = 0.040$).
Health questionnaire [8]	$N = 9239$	Those with the highest exposures (arriving morning of 9/11) were more likely to score positive on the Diabetic Neuropathy Symptom test (OR 1.35; 95% CI, 1.10–1.65) than those in the lowest exposure group (p-test for trend $p = 0.004$).
Longitudinal cohort study [52]	$N = 99$	Compared to unimpaired FR, global mean cortical thickness was reduced in cognitively impaired FR ($p < 0.05$).
[61]	$N = 198, 196$	Neurotoxic exposures from toxic composites from WTC dust produce deficits in olfaction and gustation.
Meta-analysis [45]	$N = 29{,}930$	Depressive symptoms were significantly associated with post-9/11 social isolation (OR, 1.68; 99.5% CI, 1.13 to 2.49) and knowing someone injured or killed (OR, 2.02; 99.5% CI, 1.42 to 2.89).
Cohort study [65]	$N = 8418$	Survivors caught in the dust and debris cloud were more likely to report severe headaches (AOR = 2.0; 95% CI, 1.8–2.3); hearing problems or loss (AOR = 1.7; 95% CI, 1.4–2.0); self-reported depression, anxiety, or other emotional problem (AOR = 1.4; 95% CI, 1.3–1.6); and current SPD (AOR = 2.2; 95% CI, 1.8–2.6).

While a variety of pathologies manifested in FR/recovery workers in the early years after the disaster, it has become apparent in surviving FR/recovery workers that initial high level exposures to the distinct WTC dusts also likely led to an increase in risk of long-term systemic consequences [4–7]. Thus, as surviving FR/recovery workers reach middle age or retire, their prior WTC dust exposures might expedite or make worse any age-related diseases that normally manifest in those work populations. Unfortunately, data bears this out, i.e., there are strong indications these survivors are now developing extra-pulmonary health problems at a prevalence disproportionate to that seen in non-dust exposed age-match cohorts. These include pathologies of the nervous system [8,9], cardiovascular system [10,11], immune system [12,13], and prostate [14,15] among some of the various non-lung organ/organ systems known to have been impacted (Table 1, Fig. 1).

As such, it remains imperative to continue efforts towards determining the extra-pulmonary pathophysiology associated with WTC dust inhalation. Accordingly, this review provides a comprehensive update specifically on pulmonary, cardiovascular, and neurologic sequelae that FR are increasingly experiencing, 20 years after the towers collapsed.

2. Pulmonary consequences of WTC dust exposure

First responders (FR) and recovery workers at Ground Zero were routinely exposed during the first few days to high levels of hazardous

materials in dusts generated by the collapse of the WTC towers. The types of exposures faced on those days were governed by the use/non-use of respirators, arrival time/time spent at Ground Zero, and the extent of mouth breathing while performing heavy labor. In comparison, clean-up worker exposures to smaller-diameter WTC dusts were often for prolonged periods and in an absence of any personal protective equipment [1]. Among residents who lived near Ground Zero, individual exposures (i.e., doses, longevity) were dependent on if the dusts entered through shattered windows or via building ventilation systems, if respirators were worn, as well as how quickly the dusts were cleared from each residence.

Soon after the disaster, there were documented increases in significant adverse health effects among FR/recovery workers who had been repeatedly exposed to large amounts of WTC dusts. Many FR began to experience shortness of breath, dyspnea, and wheezing [16,17]. Commonly referred to as WTC Cough, as shown in a large cohort (n = 12,781), this syndrome was characterized by severe cough and shortness of breath, followed by an acute decline in lung function [18]. In an additional cohort of 10,641 FR (65% never-smokers), 19.5% of those exposed experienced greater age-related decline in forced expiratory volume in 1 s (FEV_1), characterized by >64 ml/yr, twice the average of age-related FEV_1 decline [19]. From this same study, 66.5% of FR experienced an age-related decline in FEV_1 and 15% experienced improved FEV_1. Changes in FEV_1 differed significantly by smoking status: 32.2% of current smokers experienced greater age-related decline compared to 17% of never smokers. Treatment with inhaled steroids combined with long-acting β-agonists (ICS/LABA) was found to improve dyspnea, asthma, and COPD in these FR years after the initial WTC exposures [17]. Among these FR and recovery workers, there were also reported increases in the incidence of irritant-induced asthma, bronchitis, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis (PF) and chronic inflammation in the upper and lower airways [16,18,20–23]. As with the other above-noted health effects, the incidence of many of these disorders also strongly correlated with respirator use/non-use and arrival time and/or time spent at Ground Zero [24].

Histological studies of FR lung samples also confirmed a high incidence of sarcoid-like granulomatous lung disease (SGLD) or sarcoidosis [16,66]. Of the FR sampled, 23% had extra-thoracic adenopathy, with 3 of 26 FR with a total lung capacity or diffusion <80%. SGLD or sarcoidosis is often asymptomatic, with initial presentation of persistent dry cough, shortness of breath, and fatigue; if left untreated, SGLD/sarcoidosis may progress to multi-system organ damage (i.e., enlarged liver, pericarditis, kidney stones, heart failure). It remains unclear whether increased incidence of sarcoidosis may be exposure-related or simply due to the overall increased surveillance of the WTC FR. While to date no large numbers of cases of parenchymal or interstitial lung diseases have been described among the FR cohort, there have been isolated reports of cases of eosinophilic pneumonia, interstitial fibrosis, and granulomatous pneumonitis. Most interestingly, while there have been generalized increases in incidence of a variety of cancers in FR who were at Ground Zero for prolonged periods in the first week, none has yet to be categorically associated with exposure to the WTC dusts themselves. Of note, there remains no data indicating an association between WTC dust and lung cancers in FR; however, the latency period between exposures and detection of WTC dust-induced lung cancers likely means that a much longer-term surveillance (as with asbestos) will be required [16].

Apart from the initial dusts on 9/11, FR and other workers involved in recovery at the disaster site were exposed to both re-entrained dusts that had settled, as well as fires that burned for months (and whose chemical compositions changed over time) following the attacks. Inhalation of these various materials led to workers experiencing recurring inflammation of the mucosal surfaces of the nose, sinuses, and lungs, resulting in rhinosinusitis often associated with laryngitis and pharyngitis [18]. Among WTC recovery workers evaluated in 2007, 78.5% experienced persistent rhinitis, sinusitis, pharyngitis, and laryngitis, while 57.6% experienced gastroesophageal reflux disease (GERD) and 48.9% other lower airway diseases [25]. Onset of rhino-sinusitis occurred shortly after leaving the disaster site and presented alongside GERD ([26]). Subsequently, increased incidence of obstructive airway diseases (OAD) were found to be associated with WTC dust exposure, even 7 years after the end of any WTC-related work, suggesting that there was a latency period for OAD onset as well as some delayed diagnosis [27]. A machine learning approach, which has the ability to analyze differential expression of individual metabolites, later found that biomarkers of metabolic syndrome, vascular injury, and inflammation were all predictors of lung dysfunction, recurring inflammation, and OAD due to the original WTC dust exposures [21].

2.1. Potential mechanisms of WTC-related pulmonary consequences

Pulmonary symptoms of WTC dust exposure in FR were often reflected as cases of chronic inflammation, consequent respiratory symptoms (shortness of breath, dyspnea, wheezing), and ultimately lung dysfunction. One explanation attributes development of some of these symptoms to alterations in levels of select biomarkers of inflammation, including α1-anti-trypsin (AAT), immunoglobulin E (IgE), and eosinophils (EOS), in the lungs.

The protease inhibitor (Pi) AAT targets and inactivates neutrophil elastase. Mutations of the Pi gene produce severe deficiency in AAT levels and function, where in one study, WTC FR AAT genotype and serum levels were seen to be associated with FEV_1 decline [67]. Specifically, those FR with reduced AAT levels or AAT abnormality showed a decline in FEV_1 of 69 ml/yr, while those with moderate genetic abnormality showed a decline of 147 ml/yr. From these studies, it is clear further identification of the still-healthy FR at risk for lung dysfunction is necessary to permit any early intervention. Such data could be obtained via genetic testing for AAT genetic abnormalities as well as testing of serum AAT levels.

In contrast to ATT, changes in local EOS and IgE (that binds/activates basophils and mast cells, ultimately resulting in airway constriction) levels may indicate innate immune injury to the airways in the WTC dust-exposed FR. The data from this 2017 study showed that among these FR who had shown normal IgE serum levels prior to the WTC disaster, a subset of never-smoker FR (4%) subsequently presented with increased IgE levels (> 500 IU/ml). Each 100 IU IgE/ml increase was associated with a 38% increase in odds of abnormal FEV_1/Forced Vital Capacity (FEV_1/FVC) ratios [18]. Further investigation should be performed to examine the roles of altered levels of IgE and EOS as potential underlying causes for the declining lung function in WTC dust-exposed FR.

Lung EOS are well-defined biomarkers of innate immune local injury. Changes in lung EOS levels were associated with symptoms of asthma and OAD in a cohort of WTC dust-exposed patients who were not FR involved in Ground Zero recovery and/or residents who resided nearby. Specifically, in this group of individuals, deviations of blood EOS levels >4% of leukocytes (or > 500 cells/μl) were associated with increased wheezing; elevated EOS levels also were seen to increase the odds of abnormal FEV_1/FVC ratios by 2.4-fold [18,28].

Other possible explanations for the onset of lung injury and dysfunction in WTC dust-exposed FR/recovery workers is damage to ciliated and goblet cells, impeding the ability to clear inhaled toxicants from the airways. A study by Cohen et al. using rats exposed to Ground Zero dust via intratracheal inhalation (to simulate mouth breathing FR/recovery worker exposures) provided evidence of this mechanism [29]. Analysis of lung samples over a 1-yr period from rats showed there was a significant decrease in ciliated cell levels and an increase in hyperplastic goblet cells due to WTC-dust exposure. This finding suggested that inhaled WTC particles entrapped in the lungs altered the clearance activities of cilia; such an effect would allow increases in the periods of time for the variety of pollutants found in the WTC dust/Ground Zero air/Main Pile smoke to exert toxicities - as well as to interact with one

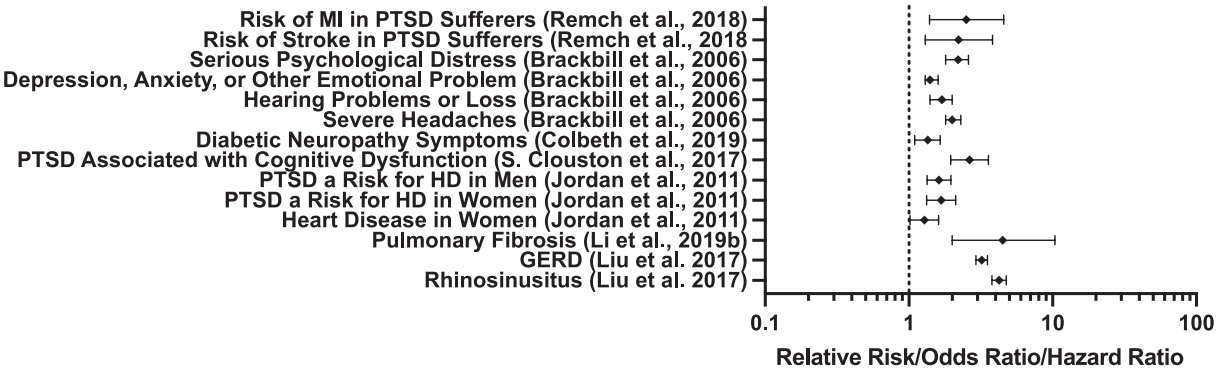

Fig. 1. Relative risks, odds ratios, or hazard ratio of selected studies. Data is shown with error bars indicating 95% CI.

another, and so increase their potential toxic impacts ([29]).

An occurrence of this mechanism in FR/recovery workers would have serious implications. There are many known cardiovascular (CV) toxicants that were present in the diesel fumes generated by trucks, cranes, and heavy equipment used in rescue and clean-up efforts. Similarly, there were many carcinogens, immunotoxicants, and neurotoxicants in metal cutting fumes generated by rescuers using arc torches to break down beams during these same rescue and clean-up efforts.

3. Cardiovascular consequences of WTC dust exposure

Environmental exposures such as those produced by the WTC disaster have become a major area of concern for the development of cardiovascular disease (CVD). There have been clear inconsistencies from observational research, evaluations, questionnaires, self-reporting, and physician examinations [6,10,30–32]). Despite association with additional comorbidities, most models show CVD, and the progression of its symptoms, occurs secondary to air pollutant exposure, pulmonary injury, metabolic syndrome, insulin resistance, and/or systemic inflammation since arterial stiffness occurs prior to CVD [10,20,31,33]. Unfortunately, the nature of these symptoms has pathological overlap, so determining mechanistic progression of occurrence poses challenges.

Although hospitalizations due to cardiac events did increase after WTC exposure, and adjusted hospitalization hazard ratios (HR) for myocardial infarction and stroke were 2.17 and 3.01, results pertaining to morbidity and mortality have been mixed. Previously, PM exposure has been associated with increases in CV morbidity and mortality [20,32,34]. Interestingly, while studies demonstrated WTC exposure duration and intensity were associated with increased all-cause mortality, CVD mortality was lower than predicted [35–37]. In a 2018 study of a cohort of 6481 FR, there were three deaths in total as a result of CVD [32]. A 2019 study of another cohort of 9796 WTC firefighters found 120 had suffered myocardial infarctions, 61 cerebrovascular accidents, 71 required coronary artery bypass grafts, 236 underwent percutaneous coronary interventions, and 1 had a congestive heart failure event; in this cohort, there was a total of six deaths during the 18-yr post-9/11 period (H. W. [10]). Taking into account both the healthy worker effect (i.e., less healthy individuals are less likely to be employed) and participation by FR in the World Trade Center Health Program (WTCHP) which provides routine medical monitoring (and so presumably earlier detection/treatment of diseases, including CVD), are likely contributing factors for these lower-than-expected CVD-related outcomes [35,37].

In WTC dust-exposed FR/recovery workers and other site workers, CT scans detected vasculopathies such as elevated pulmonary artery to aorta ratios (PAAr) [38]. These abnormalities were associated with a 1.63 increased odds of a FEV_1 less than the lower limit of normal [38]. Presence of elevated PAAr has been connected with obesity, obesity-related pulmonary hypertension, and metabolic syndrome [38]. This could also be due to PM constituents in WTC dust that managed to directly enter the circulation, thereby inducing increases in cardiac sympathetic tone and/or stimulation of lung cells to release pro-inflammatory/−oxidative markers [39]. In a mouse model, circulating levels of nitric oxide (NO, known for homeostatic role in preventing atherosclerotic events and CV pathologies within vasculature) were significantly decreased 24 h after exposure to WTC dust suspended in DPBS (doses from 31 to 4000 μg/50 μl); such outcomes were indicative of an ongoing aortic endothelial dysfunction [39]. Another study in mice reported there were increases in right atrial and pulmonary vascular pressures - along with more resistant pulmonary vascular flow - after instillation exposure of 200 μg WTC dust [33]. The same hosts also revealed impaired cardiac function and reduced myocardial contractility [33]. These aforementioned conditions may eventually result in platelet aggregation, decreased heart rate variability, and metabolic syndrome phenotypes [20], each of which can increase the risk of CVD events.

Pre-existing metabolic syndrome is known to increase general host susceptibility to inflammation and CV risk induced by exposure to PM [20]. Metabolic syndrome diagnosis occurs if a host has at least three of the five following abnormalities: abdominal obesity, high triglycerides, low HDL, high blood pressure, or elevated glucose. Studies have shown that exposure to air pollution/$PM_{2.5}$ promoted elevated glucose levels via changes in host insulin resistance, systemic inflammation, and reactive oxygen species formation, as well as inducing dyslipidemia, factors that are each linked to hypertension and metabolic syndrome [20,21]. HR for CVD resulting from risk factors such as hypertension, hypercholesterolemia, and diabetes were 1.41, 1.56, and 1.99, respectively in WTC dust-exposed FR/recovery workers [10]. One study showed FR with metabolic syndrome had associated markers related to atherosclerosis and CVD, despite their having a lower prevalence of the syndrome as compared to the national average (27 vs 45%) [31]. The physically-demanding nature of their profession and the healthy worker effect phenomenon may again be contributing to this difference [31]. Metabolic syndrome was significantly higher in male law enforcement officers compared to in female counterparts (28 vs 20%, $p = 0.001$) [31]. The presence of metabolic syndrome in various studies is noteworthy as it is often concurrently linked with an increased risk of CVD.

Perfluoroalkyl substances (PFAS), widely used in building materials (including the WTC buildings), are known to interfere with lipid metabolism, transport, communication, cholesterol synthesis. The resulting elevated lipid panels pose a potential risk for development of both atherosclerosis in particular and CVD in general. Levels of PFAS were found to be elevated in the serum of children/adolescents living in the periphery of Ground Zero, and these elevations persisted for several years after their initial WTC dust exposure(s) [40]. Of the PFAS, perfluoro-octanesulfonic acid and perfluorononanoic acid discovered in the serum of exposed individuals have both been linked to decreases in host insulin-like growth factor levels and increases in metabolic syndrome [6,40]. Despite being elevated, another WTC study did not find any significant associations between serum PFAS levels and pathologies of interest in adolescents who lived or attended school in the periphery

of Ground Zero [6,41].

When comparing equivalent levels of dioxins in WTCHP participants vs. non-participants from the 2003–2004 National Health and Nutrition Examination Survey for youth ages 12–19, mean and median concentrations were > 7-times higher in the WTCHP subjects. Elevated serum levels of polychlorinated dibenzo-*p*-dioxin and polychlorinated dibenzofuran resulting from the WTC disaster have been associated with increased incidence of diabetes and other adverse health outcomes [42]. This was the case for firefighters, National Guard members, and even pregnant women who lived near Ground Zero [42]. Another set of studies measuring dibenzo-*p*-dioxin and polychlorinated dibenzofuran in adolescents also noted elevated levels; the investigators believed their changes were a result of chronic "home dust" exposure that had persisted even up to 12 years after the 9/11 disaster [6,42].

3.1. PTSD and CVD

Since post-traumatic stress disorder (PTSD) can over-stimulate the sympathetic nervous system (resulting in release of inflammatory signals and molecules), it often precedes the onset of atherosclerosis, heart disease, heart attack, and stroke [6,30,32,34,43] Within the WTC-Heart Cohort (19.9% in men and 25.9% in women), PTSD prevalence was higher, i.e., double that of the general population [32]. The cumulative risk of myocardial infarction or stroke was also seen to be significantly higher when PTSD occurred, and this further increased over time from WTC-related trauma [32,44] A significantly-higher incidence of stroke was also present among WTCHP participants who had been diagnosed with PTSD (3.53 vs 1.64 per 1000 person-years), intense dust cloud exposure (2.33 vs 1.77 per 1000 person-years), and with both PTSD and intense exposure (4.30 vs 1.61 per 1000 person-years) [34]. Despite claiming that dust exposure duration or intensity had no effect on CVD outcomes, adjusted HR for myocardial infarction and stroke were 2.22 and 2.51; adjusted HR for stroke were independently and directly increased for PTSD (1.69) and intense dust cloud exposure (1.30) [32,34].

3.2. Murine model relationships with human outcomes

Very few interventional studies have been performed to determine direct causal mechanistic relationships between WTC dust-particulate matter exposure and potentially deleterious CV outcomes. Acknowledging these limitations, a recent study quantified various acute and chronic cardiorespiratory and vascular parameters in a murine model using echocardiography, μ-PET/μ-CT, and histology after a single 200 μg WTC dust aspiration, discovered a myriad of physiological alterations [33]. The vasculo-centric theory suggests damage to blood vessels and subsequent CVD before disease progression. In WTC dust-exposed mice, pulmonary artery mean flow velocity and peak flow velocity were significantly decreased at 24-h and 1-mo post-exposure compared to non-dust-exposed controls. Pulmonary artery acceleration time (a negatively correlated measure of pulmonary vascular resistance) was significantly decreased, as was the pulmonary acceleration to ejection ratio compared to non-dust-exposed controls. Mid-systolic notch and bidirectional blood flow were also discovered, indicating possible pulmonary valve insufficiencies, and mean pulmonary artery pressure was increased during both measurements. Despite the similarity in right ventricular stroke volume, an increase in wall thickness and decrease in internal diameter indicated cardiac hypertrophy [33]. Statistically significant hallmark indicators of CVD, such as decreased stroke volume (24-h: $p < 0.05$) and cardiac output (24-h, $p < 0.05$; 1-mo, $p < 0.01$), were discovered via the left ventricle. The possibility of aortic stiffness and blood flow reduction may have resulted from decreases in aortic ejection time, velocity time interval, and the aortic acceleration to ejection time ratio.

Using μ-PET/μ-CT, significantly elevated standard uptake values in cardiac tissue as well as increased cardiac volumes were discovered in these mice [33]. Histologic imaging found significant aortic collagen deposition from α-smooth muscle actin, presumably as a result of acquired endothelial injury and inflammation, indicative of worsening vascular pathologies. Metabolite levels for superoxide dismutase, total anti-oxidant capacity, and soluble receptor for advanced glycation end products were all significantly increased in the mice at 24-h post-exposure, implicating vascular dysfunction and pulmonary artery hypertension [33].

3.3. Relating mouse studies to FR exposures

The aforementioned mouse study found numerous pathological deficiencies subsequent to aspiration. Unfortunately, in humans, these insufficiencies are often not discovered until a major event occurs, leading to the need for medical interventions. A study of 9796 firefighters from the FDNY Medical Monitoring Program found that both early arrival on September 11 and prolonged exposure to WTC dusts (for up to ≥6-mo) resulted in higher HR (1.44 and 1.30, respectively) for primary CVD events such as myocardial infarction, cerebrovascular events, coronary artery bypass grafts, percutaneous coronary interventions, and congestive heart failure [10]. Similarly, HR for heart disease correlated in a dose-related manner to the number of injuries the FR sustained, particularly head and musculoskeletal, but not necessarily to dust exposures itself [6,43]. Perhaps in the future, real-time, non-invasive medical monitoring of similar predictive values, as measured in the mouse study, will be possible thus allowing earlier treatment and avoidance of primary CVD events and heart disease.

3.4. Expanding on limitations

Due to the inconsistencies among published epidemiological data, further research is essential to provide valuable information on the progression, occurrence, and outcomes of CVD resulting from the exposures that occurred among the FR/recovery workers as a result of the WTC disaster. Interventional research may be able to provide a mechanistic progression of CVD as either happening primarily, secondarily, or concurrent with other co-morbidities; this type of research would also provide opportunities for reproducibility and clarification of mixed results. Continued tracking of health outcomes, especially of previously WTC-exposed children and adolescents, will yield longitudinal data that will allow investigators/clinicians to better elucidate connections between WTC dust exposure and CVD. Since CVD is a progressive disease, increased duration of time from exposure from the original 9/11 disaster may result in increased morbidity and mortality data. To avoid these trajectories, further investigation of the type noted above is clearly warranted.

4. Central nervous system consequences of WTC dust exposure

Trauma associated with the WTC disaster increased the risk of depression, cognitive impairment, neurodegeneration, and heightened chances of dementia development [45,46]. In addition, the presence of known classes of neurotoxins, such as lead, aluminum, cadmium, manganese, tin, and complex hydrocarbons (i.e., polychlorinated biphenyl), within the WTC dusts is believed to have led to the documented increase in FR/individuals who now suffer from peripheral neuropathy and chemosensory dysfunctions [8].

4.1. PTSD linked to cognitive impairment

PTSD and co-morbid depression are commonly studied post-disaster health outcomes [45]. Measured with questionnaires tailored to 9/11, it was found that injury, losing someone, and witnessing horror were three of the most detrimental exposures resulting in PTSD (B. [47]). A prospective cohort study of 1193 WTC FR in 2017 found a greater risk of cognitive dysfunction compared to age-matched normative data ($d =$

0.38–0.44) [48,49]. The study further found that PTSD was associated with a moderately-increased risk of cognitive dysfunction, evidenced by slower reaction speeds, processing speeds, and worsening memory (RR = 2.64, 95% CI = [1.95–3.57]). The investigators identified an association between time working on-site and a lowered cognitive function (RR = 1.36, 95% CI = [1.03–1.80]). A 2019 study performed on 1800 WTC FR who were cognitively intact at baseline assessment, then re-assessed 1–2.5 years later (average 1.48) [50], found a higher than expected mild cognitive impairment (MCI) incidence over an 18-mo follow-up period when incidence statistics were compared to estimates among unexposed individuals from a general population of individuals who were on average 20 years older [50]. In addition to MCI, PTSD has been shown to cause functional limitations such as slowed walking, trouble getting out of a chair, and balance problems [48,49] and is associated with rapid aging and even premature senescence [51]. Though traumatic experience of the disaster may have induced cognitive dysfunction (i.e., memory impairment and lower attention), there is now evidence to suggest that neurotoxic agents within the WTC dusts may have actually been able to penetrate the blood-brain barrier (BBB) [50].

4.2. Evidence of cognitive impairment

During events of chronic stress or PTSD, the brain is challenged in a way that may lead to neurodegeneration. Evidence in combat veterans has linked chronic PTSD with cortical thinning among regions including the frontal, temporal, occipital, and insular regions [52]. It has been reported that cognitively impaired (CI) (Montreal Cognitive Assessment ≤20 to identify CI) and cognitively unimpaired (CU) WTC responders with or without PTSD had reduced cortical thickness in the entorhinal and temporal cortices, compared to published normative data [52]. To infiltrate the BBB, inhaled PM must be small (<0.1 μm), round, and smooth [50]. However, some nanoscale particles and metal elements of $PM_{2.5}$ are known to have been able to get through the BBB into the brain and cause damage (Q. [53]). Recently, Hajipour et al. [54] showed that healthy rats exposed to significant impairment of spatial cognition when the hosts were tested in a Morris water maze [54]. These rats also exhibited decreased function of hippocampal long-term potentiation due to disruptions of BBB permeability, brain edema, and increases in oxidative stress/inflammation in their brain tissues [54]. If this set of results can be extrapolated to the human scenario, then the changes noted in CI among the FR might have possibly been a result of the WTC dust causing increases in inflammatory responses and oxidative stress within their brains.

While most research today related to the WTC disaster concentrates on pulmonary exposures with the coarse/supercoarse particles of dust, it has been proposed that small, round and smooth particles in the inhaled dust that were generated during the continuing fires at Ground Zero (or even the small fraction that was present in the original pulverization of the buildings) could, over a long period, increasingly penetrate the BBB. Since rat studies have shown prolonged retention of the originally-inhaled WTC dusts, this slow release and subsequent intracranial deposition of these small particles might be determined to be a primary mechanism to explain the increases in development of neurodegeneration in the brains of the WTC FR [48–50].

These two studies by Clouston et al. went further to identify the *APOE*-ε4 allele as a causative agent in increasing the potential of developing MCI or even dementia. The *APOE*-ε4 allele is apparent in old-aged individuals; these studies reported a strong association between prolonged exposures to WTC dusts and a higher incidence of MCI among FR who also carried the *APOE*-ε4 allele. While other studies have identified a link between PTSD, CI and AD, and Alzheimer's Disease and Related Dementia (ADRD), if this also pertains to the exposed FR and others near Ground Zero remains to be determined [46,48,49,55,56].

As background, it is known that non-WTC dust-exposed PTSD patients were more than twice as likely to develop dementia during a follow-up period (median = 7.2 years) compared to those without PTSD [46]. Biomarkers, such as β-amyloid (Aβ) subtypes Aβ42 and Aβ40, Aβ42/Aβ40 ratio, total Tau (T-total), and total Aβ have been used to produce an accurate diagnosis of AD [56]. Recent animal studies showed that exposure to severe and chronic stress can lead to Aβ deposition in amyloid precursor protein transgenic mice [55]. Two recent studies of WTC dust-exposed FR suggested that reductions in total plasma Aβ load among those with PTSD or CI may be accompanied by an increase in their Aβ42/Aβ40 ratio [55,56]. From this, it is possible to conclude that in FR, there may be a decrease in Aβ40 and an increase in total Aβ compared to those without PTSD or CI. Since a majority of WTC FR are now middle age and AD is not particularly prevalent in their age groups, a link between PTSD and AD may suggest that there is an increasing potential risk for AD development among still-healthy WTC FR. To better understand this, more longitudinal assessments of neurological biomarkers with larger populations are needed [55].

4.3. Paresthesia

Paresthesia is a burning/prickling sensation in the extremities but can be present anywhere in a body. Peripheral neuropathy can result from damage to nerves outside the CNS and can occur in metabolic disorders, inflammatory diseases, or following exposure to environmental or biological toxins [8]. A 2019 study analyzed FDNY WTC Health Program data with assessments of an indicated (having conditions linked to peripheral neuropathy) (n = 2059) and a non-indicated group (n = 7180) [8]. In the latter, 23.8% reported ≥1 symptom of peripheral neuropathy, compared with 31% of those with co-morbid conditions known to be associated with paresthesia, specifically diabetes, cancer, or autoimmune disease [8]. Additionally, among WTC survivors, there was a significantly shorter time to onset of paresthesia among persons who had jobs that required cleaning of WTC dust, or who were immensely covered with dust on the day of the disaster [57].

To identify whether WTC dust has a direct impact on nerve injury, additional studies are warranted. This type of research began with a pilot study identifying effects of WTC dust exposure on rat sciatic nerves [58]. The study preliminarily concluded the causative agents may be hydrocarbons in the dusts, as there were significant reductions in conduction velocity of nerves exposed to the dust in vitro [58]. Using electrodiagnostic neurological measurements, another study showed that intraepidermal nerve fiber densities were below normal in 47% of WTC-exposed paresthesia cases and sural to radial sensory nerve amplitude ratios were < 0.4 in 29.4% [59]. Having nerve amplitude ratios <0.4 are abnormal and suggest a diagnosis of axonal polyneuropathy [59]. Though many questionnaires and screenings have been conducted, more objective measures such as EMG studies, skin biopsies and use of animal models, are needed to confirm any causative roles for the dusts in the now-documented cases of WTC dust-exposed paresthesia [60].

4.4. Chemosensory dysfunction

Those individuals who were involved in the prolonged rescue and clean-up operations at Ground Zero in the weeks/months after the disaster were often exposed to settled dusts that had been re-entrained, as well as toxic materials released by the fires that burned within the Main Pile for months. While paresthesia was reported in WTC dust-exposed FR/recovery workers, chemosensory dysfunction (associated with olfaction and gustation/taste) was also shown to have occurred among clean-up workers exposed to the materials [61]. One study showed that the prevalence of olfactory and trigeminal nerve sensitivity loss was significantly greater in WTC dust-exposed workers relative to a comparison group [prevalence ratios (95% CI) = 1.96 (1.2–3.3) and 3.28 (2.7–3.9) for odor and irritation thresholds, respectively] [62]. In irritation threshold tests, nearly 75% of the WTC-exposed workers exhibited scores below the normal range (i.e., below dilution step 4 for *n*-butanol) compared with 23% in a control group [62]. In addition,

nasal lavage samples revealed there was ongoing chronic inflammation in the WTC cohort, and that these changes were associated with increased local levels of interleukin (IL)-8 as compared to lavage samples of the controls. Of all the FR/recovery workers and other individuals who worked and/or resided near Ground Zero, those who had been trapped in the original dust cloud and those exposed to dusts for the longest times exhibited the most profound trigeminal sensitivity loss measured with an irritant threshold test (n-butanol) [62]. Taking these conclusions into account, it is clear a fuller analysis of nasal tissue is needed to characterize mechanisms underlying this loss of smell. While one may not consider it an overtly major health risk, ultimately, a lack of olfactory warning signals will have a significant impact on nutritional status, eating satisfaction, and issues related to quality of life of these affected in FR/other exposed individuals.

It is evident there is a correlation between cognitive impairment and WTC dust-exposed FR/recovery workers, most likely due to PTSD and the presence of a variety of neurotoxins in the dusts that were released as the towers collapsed. Further longitudinal studies are needed regarding AD biomarkers in the WTC FR as a whole. In addition, many dust-exposed individuals have suffered from paresthesia, as well as olfactory and gustation dysfunction. Additional investigation of those individuals and underlying mechanisms of causation are needed. Lastly, it is strongly recommended that animal models be emphasized for future studies that are being undertaken to research the variety of peripheral nervous system problems associated with WTC dust exposures.

5. Conclusions

A summary of the major pulmonary, cardiovascular, and neurologic health sequelae arising from exposures to the WTC dusts is shown in the Table and Figure. As can be referenced from the studies cited, the acute effects from exposures to WTC dusts are now well-documented. However, the long-term health effects remain unclear.

To better treat those that risked their lives during and after the disaster of September 11, 2001, the deleterious mechanisms that WTC dust exposure exerted and continue to exert on the heart, lungs, and brain of FR must be better understood.

CRediT authorship contribution statement

Matthew J. Mears: Conceptualization, Writing-Original draft preparation. **David M. Aslaner**: Writing- Original draft preparation. **Chad T. Barson**: Writing-Original draft preparation. **Mitchell D. Cohen**: Writing-Reviewing an editing. **Matthew W. Gorr**: Writing-Original draft preparation. **Loren E. Wold**: Supervision, Writing-Reviewing and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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