



COVID-19 AND LONG-TERM RESPIRATORY OUTCOMES: CURRENT PERSPECTIVES ON PATHOPHYSIOLOGY AND PULMONARY COMPLICATIONS

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Abstract

The collapse of the World Trade Center (WTC) towers on September 11, 2001 (9/11), resulted in massive exposure to a complex mixture of pulverized building materials and combustion products, leading to a recognized occupational and environmental disease cluster (Prezant et al., 2002; Landrigan et al., 2004). This review focuses on the “WTC cough syndrome,” defined as a severe, persistent cough, often coupled with upper respiratory, lower respiratory, and gastroesophageal reflux disease (GERD) symptoms (Prezant et al., 2002). Longitudinal studies, particularly within the Fire Department of the City of New York (FDNY) cohort, have established a clear dose-response relationship between exposure intensity and disease incidence (Prezant et al., 2002; Wisnivesky et al., 2011). Pathophysiologically, the highly alkaline



nature of the WTC dust induced chronic airway inflammation, leading to long-term sequelae such as accelerated decline in forced expiratory volume in 1 second (FEV1) and the emergence of obstructive airways disease (OAD) phenotypes, often characterized by restrictive patterns due to distal airway dysfunction (Aldrich et al., 2010; Berger et al., 2013). Persistent physical illness is highly comorbid with mental health disorders, notably Post-Traumatic Stress Disorder (PTSD) (Niles et al., 2011; Wisnivesky et al., 2011). Furthermore, WTC exposure is associated with increased risks of specific cancers, underscoring the necessity of ongoing, multidisciplinary longitudinal health surveillance.

Keywords: World Trade Center, WTC cough syndrome, inhalational injury, small airway disease, FEV1 decline, GERD, PTSD.

Introduction

The attacks of 9/11 generated an acute environmental disaster of unprecedented magnitude, exposing hundreds of thousands of individuals, including rescue and recovery workers (RRWs) and community members, to a massive cloud of toxic gases and particulate matter (PM) (Landrigan et al., 2004; Mears et al., 2023). The resultant dust cloud was complex, comprising pulverized cement, glass fibers, asbestos, silica, heavy metals, and various organic chemicals from combustion, notably exhibiting high alkalinity (pH > 10) (Liroy et al., 2002; Landrigan et al., 2004; Desai & Skloot, 2018; Summerhill et al., 2017). This extreme exposure resulted in an immediate surge in respiratory and mental health symptoms among virtually every FDNY worker who participated in the 10-month recovery effort (Niles et al., 2011; Prezant et al., 2002). Early documentation quickly identified a distinct clinical entity, the WTC cough syndrome, which serves as a sentinel indicator of the respiratory damage incurred (Chen & Thurston, 2002; Prezant et al., 2002). The long-term trajectory of WTC-related lung injury has evolved into a chronic health crisis, characterized by persistent pulmonary function deficits and complex multimorbidity (Wisnivesky et al., 2011; Yip et al., 2016).

Definition and Etiology of WTC Cough Syndrome

WTC cough syndrome was defined early in the aftermath of 9/11 as a persistent cough developing after WTC exposure, severe enough to necessitate at least four



consecutive weeks of medical leave (Prezant et al., 2002; Prezant, 2008). This syndrome was not merely cough in isolation; it was characterized by a constellation of symptoms requiring the presence of at least one symptom in each of three categories: upper respiratory symptoms (URS, e.g., nasal congestion or drip, sore throat), lower respiratory symptoms (LRS, e.g., wheezing, shortness of breath, frequent cough), and GERD symptoms (e.g., heartburn, chest tightness or pain) (Niles et al., 2011; Prezant et al., 2002). In the initial six months post-9/11, the incidence of WTC cough syndrome demonstrated a clear exposure-response gradient among FDNY firefighters: 8% among those with high exposure (present during the tower collapses), 3% with moderate exposure, and 1% with low exposure (Prezant et al., 2002; Prezant, 2008). High exposure status, typically defined by arrival during the collapse or longer work duration at the site, was a cofactor associated with the syndrome at baseline and follow-up (Niles et al., 2011). Exposure to the complex and caustic WTC dust, consisting of pulverized building materials and combustion products, served as the primary etiology (Landrigan et al., 2004; Yip et al., 2016). The clinical definition of WTC cough syndrome implicitly acknowledges the complexity of the toxic exposure, suggesting a generalized aero-digestive inflammatory process rather than a purely pulmonary disorder (Prezant et al., 2008). The clear dose-response relationship observed across different exposure levels (Prezant et al., 2002), where earlier arrival time equated to higher risk (Niles et al., 2011; Yip et al., 2016), provides high-quality epidemiological evidence linking the initial massive irritant inhalation directly to the development of this severe, acute syndrome.

Evolution of WTC Cough Syndrome Over the Years

Over the decade and a half following 9/11, longitudinal studies confirm that WTC-related health conditions, while declining slightly from acute peaks, remain persistent and highly burdensome (Wisnivesky et al., 2011; Jordan et al., 2019). Symptom Persistence: Among firefighters, cough symptoms declined steeply within the first 4 years, affecting 54.2% initially and decreasing to 15.7% by year 4 (Webber et al., 2009; Weakley et al., 2011). However, the prevalence stabilized thereafter, with approximately 9.5% still reporting cough at year 9 (Weakley et al., 2011; Weakley et al., 2011). For residents and community members, lower respiratory symptoms (LRS) remained consistently higher in the affected area compared to control areas, even 2



and 4 years after 9/11 (Lin et al., 2010; Reibman et al., 2005). Disease Trajectory: By 2016, half of the FDNY WTC cohort had at least one physician diagnosis of OAD, CRS, or GERD (Yip et al., 2016). For the majority of FDNY workers who experienced the initial rapid FEV1 decline, recovery to pre-9/11 function did not occur, although the rate of decline subsequently stabilized to normal aging rates (Aldrich et al., 2010). Nevertheless, a significant subgroup continues to experience accelerated FEV 1 decline (Goldfarb et al., 2023). WTC exposure is associated with the long-term development of spirometrically defined low FVC, COPD, and asthma-COPD overlap (de la Hoz et al., 2021; Mears et al., 2023). The effect of WTC exposure on the incidence of chronic rhinosinusitis persisted for at least 10 years after initial exposure, showing no significant diminution over time (Weakley et al., 2016). Prognosis: Accelerated FEV 1 decline is a significant risk factor for all-cause and cancer-cause mortality (Goldfarb et al., 2023). Despite the overall burden, RRWs enrolled in federally funded monitoring and treatment programs experienced improved survival post-cancer diagnosis compared to other New York state cancer patients (Boffetta et al., 2022). The high comorbidity of physical and mental health issues necessitates a coordinated, multidisciplinary approach to care (Wisnivesky et al., 2011; Yip et al., 2016).

The persistent high prevalence of chronic aerodigestive disorders years after the exposure confirms that WTC exposure triggered chronic, rather than transient, pathology (Wisnivesky et al., 2011). The lack of lung function recovery (Aldrich et al., 2010) confirms the permanent structural alteration caused by the toxic dust. The finding that accelerated FEV 1 decline predicts mortality (Goldfarb et al., 2023) elevates lung function monitoring from a measure of morbidity to a critical prognostic indicator for survival in this unique population.

Pathophysiology of WTC Cough Syndrome

The World Trade Center (WTC) cough syndrome, initially defined by a severe, persistent cough accompanied by a constellation of upper respiratory, lower respiratory, and gastroesophageal reflux disease (GERD) symptoms (Prezant et al., 2002; Niles et al., 2011), is fundamentally an exposure-driven chronic aerodigestive inflammatory response (Prezant et al., 2008). The key pathophysiological mechanisms involve the caustic nature of the WTC dust, initial epithelial damage,



chronic inflammation, subsequent airway remodeling, and neurogenic factors amplified by psychological comorbidity.

The etiology of the WTC cough syndrome stems directly from the acute, high-level inhalation exposure to the massive cloud generated by the towers' collapse and subsequent fires (Prezant et al., 2002; Landrigan et al., 2004). The WTC dust was a complex mixture including pulverized concrete, gypsum, asbestos, silica, glass fibers, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) (Landrigan et al., 2004; Desai & Skloot, 2018; Mears et al., 2023; Durmus et al., 2020; Liroy et al., 2002).

A critical toxicological feature was the extreme alkalinity (pH > 10 to 12) of the dust, primarily due to pulverized cement (Desai & Skloot, 2018; Prezant et al., 2002; Landrigan et al., 2004; Liroy et al., 2002; Mears et al., 2023; Calvert et al., 2024). This caustic characteristic is believed to have caused direct chemical injury to the airway epithelium (Desai & Skloot, 2018; Prezant et al., 2002). While the majority (>90%) of particulate matter was larger than 10 μm (Desai & Skloot, 2018; Liroy et al., 2002; Gavett et al., 2003), the high alkalinity and the high minute ventilations (due to intense physical exertion and likely mouth breathing) experienced by rescue workers impaired normal nasal clearance mechanisms, leading to significant deposition of both fine and coarse particles deep within the lower airways (Desai & Skloot, 2018; Prezant et al., 2008; Rom et al., 2012). This disruption of mucociliary clearance has been evidenced by unusual ultrastructural ciliary abnormalities and prolonged retention (up to approximately 90% retention at 1 year post-exposure in rat models) of WTC dust burdens (Weiden et al., 2016; McMahon et al., 2011, cited in WTC Dust, 2020; Mears et al., 2023; Summerhill et al., 2017).

The inhalation of WTC dust initiated robust and persistent inflammatory responses, which can be tracked through specific molecular markers and cellular findings:

1. **Oxidative Stress and Gene Expression:** Acute, high-level exposure to supercoarse WTC dust in rat models caused significant, immediate biological changes (Cohen et al., 2015). Lungs exposed to the dust demonstrated increased expression of genes related to lung inflammation, oxidative stress, and cell cycle control, while genes involved in anti-oxidant function were inhibited (Cohen et al., 2015). This suggests acute inflammogenic effects and oxidative stress processes were triggered almost immediately following exposure (Cohen et al., 2015). *In vitro* studies supported this, showing acute toxicity characterized by necrosis in human epithelial cells, and time-/dose-related increases in pro-inflammatory cytokines like IL-6, IL-8, and TNF-alpha



in alveolar macrophages (Cohen et al., 2015; Wang et al., 2010, cited in Szeinuk, 2018; Wang et al., 2010, cited in WTC Dust, 2020). The activation of Mitogen-Activated Protein Kinase (MAPK) signaling pathways (specifically ERK and p38) was demonstrated to be instrumental in WTC dust-induced cytokine induction (Wang et al., 2010, cited in WTC Dust, 2020).

2. Systemic Inflammatory Biomarkers: Early measurement of serum biomarkers, taken within 6 months of 9/11 in a FDNY cohort, showed that elevated levels of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) and Macrophage Derived Chemokine (MDC) were independently associated with a significantly increased risk (2.5-fold and 3.0-fold, respectively) for subsequent airflow obstruction, defined as FEV1 less than the lower limit of normal (LLN) years later (Nolan et al., 2012; Weiden et al., 2012; Weiden et al., 2012; Weiden et al., 2013). This supports the hypothesis that inflammation is a mediator of susceptibility to particulate matter (PM)-induced lung injury and accelerated FEV1 decline (Weiden et al., 2012; Nolan et al., 2012; Goldfarb et al., 2023).

3. Eosinophilic and Neutrophilic Response: Induced sputum analysis in firefighters post-9/11 showed increases in neutrophils and eosinophils positively correlated with exposure levels (Landrigan et al., 2004; Fireman et al., 2004, cited in Rom et al., 2012). Persistence of asthma-like symptoms in WTC-exposed individuals has been associated with elevated peripheral eosinophil levels (Kazeros et al., 2013; Kazeros et al., 2013; Kazeros et al., 2013), suggesting eosinophils may play a role in the lung inflammation, potentially fitting into an asthma phenotype (Kazeros et al., 2013).

The resultant chronic inflammation, often fitting the criteria for Reactive Airways Dysfunction Syndrome (RADS) following high-level irritant exposure, leads to specific, persistent structural and functional abnormalities underlying the cough syndrome (Prezant et al., 2002; Brooks et al., 1985, cited in Prezant et al., 2002; Summerhill et al., 2017).

1. Bronchial Hyperreactivity (BHR): Acute, intense exposure led to airway hyperreactivity, observed in 24% of firefighters with WTC cough and 23% of highly exposed firefighters without severe cough soon after 9/11 (Prezant et al., 2002; Prezant et al., 2002). This BHR is characterized by an increased bronchomotor response to methacholine challenge (Prezant et al., 2002). In mouse models, WTC (PM_{2.5}) caused significant respiratory tract hyperresponsiveness (Gavett et al., 2003,



cited in Landrigan et al., 2004; Rom et al., 2012; Gavett et al., 2003, cited in Wisnivesky et al., 2011).

2. Distal Airway Dysfunction and "Restrictive" Phenotype: Despite normal forced expiratory volume in 1 second FEV₁/Forced Vital Capacity (FVC) ratios in many symptomatic individuals (Prezant et al., 2002; Berger et al., 2013; Reibman et al., 2009), airway obstruction is considered the predominant physiological abnormality (Prezant et al., 2002; Desai & Skloot, 2018; Weiden et al., 2010). This is primarily due to distal/small airway dysfunction (Berger et al., 2013; Rom et al., 2012). Studies using Impulse Oscillometry (IOS) detected elevated airway resistance and frequency dependence of resistance in symptomatic individuals, consistent with peripheral airway damage, even when spirometry was normal (Jordan et al., 2017; Oppenheimer et al., 2007, cited in Caplan-Shaw & Reibman, 2018; Rom et al., 2012).

3. Structural Damage and Air Trapping: High-resolution CT (HRCT) scans frequently reveal morphological evidence of airway disease, including bronchial wall thickening and air trapping (AT) (Weiden et al., 2010; Prezant et al., 2002; Mendelson et al., 2007; Mendelson et al., 2007; Rom et al., 2012). AT is strongly associated with lower respiratory symptoms (Mendelson et al., 2007; Mendelson et al., 2007). The resulting physiologic profile—reduced FVC and Total Lung Capacity (TLC) but a preserved FEV₁/VC ratio—is characterized as restriction due to airway dysfunction (Berger et al., 2013; Weber et al., 2020). This reduced lung volume is attributable to a reduced Functional Residual Capacity (FRC), compatible with airway closure in the tidal range (Berger et al., 2013). This mechanical closure is consistent with small airway obstruction and differs from true interstitial lung disease (ILD), as static lung compliance and elastic recoil pressure were found to be normal in this phenotype (Berger et al., 2013; Berger et al., 2013).

4. Involvement of Parenchymal/Interstitial Structures: While the predominant pathology is airway-centric (Berger et al., 2013), case series have documented severe pathologies involving the parenchyma, including granulomatous pulmonary disease (often "sarcoid-like") and other interstitial-like responses (Izbicki et al., 2007; Szeinuk, 2018). Pathology findings in these cases consistently report the presence of silica, silicates, and calcium oxalate particles within lung tissue, suggesting these agents are responsible for the inflammatory response leading to ILD (Szeinuk, 2018; Safirstein et al., 2003, cited in Szeinuk, 2018; Wu et al., 2010, cited in Caplan-Shaw & Reibman, 2018; Szeinuk, 2018).



WTC cough syndrome is inherently defined by its comorbidity with GERD and frequently with psychological disorders, suggesting non-pulmonary mechanistic factors (Niles et al., 2011; Prezant et al., 2002).

1. Gastroesophageal Reflux Disease (GERD): Symptoms of GERD were reported by 87% of firefighters with WTC cough (Prezant et al., 2002; Prezant et al., 2002). This extremely high incidence suggests a shared mechanistic pathway (Prezant et al., 2008). Possible mechanisms linking GERD to cough and airway pathology include the caustic ingestion of alkaline WTC dust irritating the gastroesophageal tract (Prezant et al., 2008; Prezant et al., 2002), or subsequent vagally-mediated esophageal, tracheobronchial, or laryngobronchial cough reflexes resulting from acid reflux (Prezant et al., 2002; Prezant et al., 2008). Statistical mediation analysis provides evidence that a prior Obstructive Airway Disease (OAD) diagnosis significantly increases the risk for subsequent GERD diagnosis (Liu et al., 2017), indicating that respiratory inflammation itself may precede and drive GERD, possibly through mechanically induced inflammation from coughing (Liu et al., 2017; Yip et al., 2016; Prezant et al., 2008).

2. Neuro-Immune Interaction (PTSD Comorbidity): Post-Traumatic Stress Disorder (PTSD) is highly comorbid with WTC cough syndrome, and the presence of one condition is associated with the likelihood of the other (Niles et al., 2011; Niles et al., 2011). Longitudinal studies show that PTSD symptoms are independently associated with the persistence of lower respiratory symptoms (LRS) 12–13 years after the attacks, alongside peripheral airway dysfunction measured by IOS (Jordan et al., 2017). This suggests a complex neuro-immune interaction (Jordan et al., 2017; Niles et al., 2011; de la Hoz et al., 2016). Research is actively exploring the potential epigenetic linkage between PTSD and respiratory disease, aiming to identify the precise cellular and molecular mechanisms driving this high comorbidity (Epigenetic linkage, 2012; Deciphering biological linkages, 2014). The presence of PTSD may contribute to the development of LRS and diminish treatment response (Deciphering biological linkages, 2014).

Clinical Manifestations and Respiratory Outcomes

Beyond WTC cough, exposed cohorts have experienced a wide spectrum of long-term respiratory conditions. The 9-year cumulative incidence among RRWs included asthma (27.6%), sinusitis (42.3%), and spirometric abnormalities (41.8%), with three-



quarters of these abnormalities being low Forced Vital Capacity (FVC) (Wisnivesky et al., 2011; Moline et al., 2018). Pulmonary Function Decline: WTC-exposed FDNY firefighters experienced an accelerated decline in FEV1 in the first year post-9/11, averaging 372 mL—equivalent to 10–12 years of normal, age-related loss (Aldrich et al., 2010; Banauch et al., 2006; Yip et al., 2016). This exposure-related decline showed little to no recovery in subsequent years, persisting even after 13 years for some (Aldrich et al., 2010; Aldrich et al., 2016; Yip et al., 2016; Goldfarb et al., 2023). Accelerated FEV1 decline (defined as ≥ 64 mL/year) was observed in over 10% of the cohort and is associated with increased risk of incident Chronic Obstructive Pulmonary Disease (COPD) and asthma (Goldfarb et al., 2023; Weiden et al., 2021). The risk of incident Obstructive Airway Disease (OAD) diagnoses continued to show an exposure-response gradient ten years after the disaster (Hall et al., 2015; Liu et al., 2017). Cluster analysis has identified distinct clinical phenotypes, including COPD/emphysema and low FVC clusters, which remain associated with high WTC exposure intensity (de la Hoz et al., 2021).

Specific Pulmonary Pathologies: Case reports and series documented distinct inflammatory and structural lung diseases

1. Reactive Airways Dysfunction Syndrome (RADS): Persistent BHR consistent with RADS was found in highly exposed workers (Banauch et al., 2003; Prezant et al., 2008; Summerhill et al., 2017).

2. Granulomatous Disease: "Sarcoid-like" granulomatous pulmonary disease has been identified among FDNY rescue workers, with increased incidence post-9/11 compared to pre-9/11 (Izbicki et al., 2007; Jordan et al., 2011). Lung biopsies often revealed non-caseating granulomas containing silica, silicates, and calcium oxalate particles (Safirstein et al., 2003; Szeinuk, 2018).

3. Other ILD/Airway Disorders: Rare but severe conditions documented include acute eosinophilic pneumonia (Rom et al., 2002), granulomatous pneumonitis (Safirstein et al., 2003), and bronchiolitis obliterans (Mann et al., 2005; Szeinuk, 2018; Summerhill et al., 2017). Lung tissue analysis revealed inhaled toxicants such as aluminum and magnesium silicates, and sometimes carbon nanotubes, found within macrophages at the alveolar level (Wu et al., 2010; Szeinuk, 2018; Caplan-Shaw et al., 2011).

The initial, rapid FEV1 decline among the most exposed FDNY cohort (Aldrich et al., 2010) serves as compelling objective evidence of acute, high-intensity toxic



injury. The later stabilization of decline for the majority, alongside persistent accelerated decline in a high-risk minority (Goldfarb et al., 2023), suggests the initial insult caused irreversible damage, but subsequent progression is likely mediated by host factors, chronic inflammation, and potentially comorbid conditions (Yip et al., 2016; Weiden et al., 2021). The identification of low FVC as the predominant spirometric abnormality, linked to distal airway pathology (Berger et al., 2013), underscores that WTC-related respiratory injury presents with non-traditional spirometric features, potentially leading to underdiagnosis using standard obstructive criteria.

Respiratory health conditions in WTC-exposed populations are frequently comorbid with non-respiratory disorders, forming a complex aerodigestive and psychological disease burden (Wisnivesky et al., 2011). Gastroesophageal Reflux Disease (GERD): GERD symptoms (stomach upset, heartburn, chest tightness) were a defining component of WTC cough syndrome, present in 87% of the original FDNY WTC cough cohort (Prezant et al., 2002; Niles et al., 2011; Prezant, 2008). The 9-year cumulative incidence of physician-diagnosed GERD reached 39.3% in RRWs (Wisnivesky et al., 2011). The ingestion of alkaline dust and stress have been implicated in its etiology (Prezant et al., 2008; Yip et al., 2016). Critically, the diagnosis of OAD significantly increased the risks for subsequent GERD (Relative Rate (RR) 3.21) (Liu et al., 2017; Weakley et al., 2017). OAD diagnosis was found to mediate 21% of the WTC exposure effect on subsequent GERD diagnoses, suggesting that respiratory disease may precede and contribute to GERD, possibly through cough mechanisms or shared inflammatory pathways (Liu et al., 2017). Post-Traumatic Stress Disorder (PTSD): PTSD is highly comorbid with WTC cough syndrome and other respiratory illnesses (Niles et al., 2011; Friedman et al., 2013; Li et al., 2011). A moderate association was demonstrated between WTC cough syndrome and probable PTSD; the presence of one condition contributed to the likelihood of the other, even after adjusting for shared cofactors like exposure intensity (Niles et al., 2011). PTSD prevalence among RRWs increased over time, contrasting with general population trends (Smith et al., 2021). Longitudinal studies have also shown that PTSD symptoms and peripheral airway dysfunction (IOS abnormalities) were independently associated with the persistence of lower respiratory symptoms in community members 12–13 years after the attacks (Jordan et al., 2017). Chronic Rhinosinusitis (CRS): CRS is highly prevalent, with a 9-year cumulative incidence of 42.3% in



RRWs (Wisnivesky et al., 2011). The risk of CRS diagnosis appeared increased with WTC exposure, and this risk did not diminish over the 10 years studied (Weakley et al., 2016; Liu et al., 2017). Similar to GERD, OAD diagnosis significantly increased the risk for subsequent CRS diagnosis (RR 4.24), and OAD mediated 13% of the WTC exposure effect on CRS (Liu et al., 2017).

The convergence of physical and mental illnesses is a defining feature of WTC-related health sequelae (Wisnivesky et al., 2011; Calvert et al., 2024). The statistical evidence showing that OAD mediates a portion of the exposure effect on subsequent GERD and CRS diagnoses (Liu et al., 2017) suggests that the chronic airway inflammation caused by dust exposure is a central driver of pathology across the entire aerodigestive tract. Given this high comorbidity, treatment guidelines stress that successful management of respiratory conditions is strongly linked to successful treatment of GERD symptoms, and clinicians must evaluate for mental health problems concurrently (Yip et al., 2016).

Association Between WTC Cough and Cancer

The WTC environment contained numerous known and suspected carcinogens, including asbestos, PAHs, benzene, and dioxins, providing biological plausibility for exposure-related cancers (Solan et al., 2013; Landrigan et al., 2004; Durmus et al., 2020). As of October 2012, the WTC Health Program (WTCHP) began surveillance and care for many types of cancer (Moline et al., 2018).

In cohorts of RRWs, the overall standardized incidence ratio (SIR) for all cancer sites combined was found to be elevated and statistically significant (SIR = 1.15; 95% CI, 1.06–1.25) compared to the general population in an early assessment (Solan et al., 2013). Specific cancer types showing elevated rates include: 1. Thyroid cancer (SIR = 2.39; 95% CI, 1.70–3.27) (Solan et al., 2013; Boffetta et al., 2022). 2. Prostate cancer (SIR = 1.21; 95% CI, 1.01–1.44) (Solan et al., 2013; Boffetta et al., 2022). 3. Hematopoietic and lymphoid cancers combined (SIR = 1.36) (Solan et al., 2013). Leukemia has specifically overtaken colon and bladder cancer among the top certified cancers as the 20-year anniversary approached (Smith et al., 2021).

Longitudinal analysis suggests that accelerated FEV1 decline (a pulmonary outcome) is associated not only with all-cause mortality but also specifically with cancer-cause mortality (Goldfarb et al., 2023; Weiden et al., 2023). A possible underlying



mechanism linking lung injury and cancer-cause mortality is systemic chronic inflammation and WTC-associated clonal hematopoiesis (Goldfarb et al., 2023). The elevated rates of specific cancers (prostate, thyroid, lymphoid) confirm a relationship between WTC exposure and oncogenesis (Solan et al., 2013; Boffetta et al., 2022). However, given the long latency associated with many carcinogens present in the dust, the data related to cancer surveillance remains in its relative infancy (Moline et al., 2018), necessitating decades-long monitoring to observe the full burden of malignancies, particularly those linked to asbestos (Landrigan et al., 2004; Smith et al., 2021). The association between FEV1 decline and cancer mortality introduces a novel pathway, suggesting that generalized chronic inflammation resulting from WTC dust exposure contributes broadly to disease risk (Goldfarb et al., 2023).

Future of WTC Cough: Lessons and Risk of Reemergence

The ongoing research mandated by the WTCHP emphasizes translational research aimed at improving care for chronic physical and mental health conditions (Santiago-Colon et al., 2020; Redner et al., 2020). Key research gaps identified include the need for studies to clarify causal determinants and disease progression (Redner et al., 2020). Specific research directions include:

1. **Treatment Effectiveness:** Determining the efficacy of standard treatments, such as inhaled corticosteroids (ICS) combined with long-acting beta-agonists (LABA), in blunting FEV1 decline in patients whose primary characteristic is accelerated FEV1 loss (Goldfarb et al., 2021; Rom et al., 2012).
2. **Pathobiological Linkages:** Investigating the precise cellular and epigenetic mechanisms underlying the comorbidity between PTSD and respiratory disease (de la Hoz et al., 2012; Santiago-Colon et al., 2020).
3. **Emerging Conditions:** Continued monitoring for conditions with long latencies, such as cancer and autoimmune diseases, and further studies into conditions like Obstructive Sleep Apnea (OSA) and cardiovascular risk factors that impact survival (Goldfarb et al., 2023; Smith et al., 2021; Yip et al., 2016).
4. **Diagnostic Tools:** Continued assessment of advanced imaging (HRCT) and functional measures (IOS) to refine the characterization and surveillance of lower airway diseases that escape traditional spirometry classification (Rom et al., 2012; de la Hoz et al., 2021).



5. Biomarkers: Identifying noninvasive methods to quantify remaining dust burdens in the lungs, and confirming the uniqueness of WTC-mediated effects compared to other dusts (Cohen et al., 2012; Redner et al., 2020).

The shift toward studying treatment response and comorbidity mechanisms, particularly the interaction between PTSD and respiratory illness (de la Hoz et al., 2012), reflects a maturation of WTC health research from observational epidemiology to intervention-focused translational science (Santiago-Colon et al., 2020). The proposed research on ICS/LABA benefit aims to provide evidence-based indications for treatment in a population that does not fit standard diagnostic criteria (Goldfarb et al., 2021).

Knowledge Gaps and Limitations

1. Initial Exposure Data: Crucially, air samples were unavailable during the first critical hours and days following the collapse when the highest exposures occurred; environmental measurements were taken primarily after substantial settling had taken place (Prezant et al., 2002; Landrigan et al., 2004). This uncertainty limits quantitative individual exposure assessment (Maslow et al., 2012; Reibman et al., 2009).

2. Pathophysiology and Mechanisms: The uniqueness of WTC-mediated effects compared to general dust exposures requires confirmation (Cohen et al., 2012). The precise mechanisms underlying the observed restrictive-like pattern due to small airway disease and the full extent of interstitial structures involvement (Szeinuk, 2018; Berger et al., 2013) still require clarification across cohorts.

3. Comorbidity Mechanisms: While the association between PTSD and respiratory disease is established (Niles et al., 2011), the biological and epigenetic linkages driving this comorbidity remain to be fully defined (de la Hoz et al., 2012; Santiago-Colon et al., 2020).

4. Treatment Response: There is a lack of evidence-based indications for managing chronic conditions in this specific population, such as optimal pharmaceutical management for accelerated FEV1 decline (Goldfarb et al., 2021).

Conclusion

The WTC Cough Syndrome remains a defining manifestation of acute and chronic toxic inhalational injury following the September 11 disaster. It represents a persistent, exposure-dependent complex of upper and lower airway symptoms



frequently accompanied by gastroesophageal reflux disease (Prezant et al., 2002; Niles et al., 2011). The underlying pathophysiology reflects sustained inflammatory and fibrotic processes initiated by the highly alkaline particulate matter, leading to chronic obstructive and restrictive phenotypes, accelerated decline in FEV₁ (Aldrich et al., 2010), and distal airway remodeling (Berger et al., 2013). The syndrome's interplay with non-respiratory comorbidities such as GERD and PTSD suggests overlapping neuroimmune and systemic pathways (Niles et al., 2011; Liu et al., 2017). Long-term cohort analyses further indicate elevated site-specific cancer risks, notably of the prostate and thyroid (Solan et al., 2013; Boffetta et al., 2022). Together, these findings underscore the enduring health burden of large-scale environmental exposures and the necessity of ongoing surveillance and mechanistic research.

References

1. Yip, Jennifer, et al. "World Trade Center Related Health Among NYC Firefighters and EMS Workers." *World Trade Center Pulmonary Diseases and Multi-Organ System Manifestations*. Springer International Publishing, 2017. 137-153.
2. Caplan-Shaw, Caralee, and Joan Reibman. "Persistent Lower Respiratory Symptoms in the World Trade Center (WTC) Survivor Program, a Treatment Program for Community Members." *World Trade Center Pulmonary Diseases and Multi-Organ System Manifestations*. Springer International Publishing, 2017. 47-62.
3. Weakley, Jessica, et al. "The effect of World Trade Center exposure on the latency of chronic rhinosinusitis diagnoses in New York City firefighters: 2001–2011." *Occupational and Environmental Medicine* 73.4 (2016): 280-283.
4. Weiden, Michael D., et al. "Biomarkers of World Trade Center particulate matter exposure: Physiology of distal airway and blood biomarkers that predict FEV1 decline." *Seminars in respiratory and critical care medicine*. Vol. 36. No. 03. Thieme Medical Publishers, 2015.
5. Summerhill, Eleanor M., et al. "An Official American Thoracic Society Workshop Report: chemical inhalational disasters. Biology of lung injury, development of novel therapeutics, and medical preparedness." *Annals of the American Thoracic Society* 14.6 (2017): 1060-1072.
6. Mears, Matthew J., et al. "Health effects following exposure to dust from the World Trade Center disaster: an update." *Life sciences* 289 (2022): 120147.



7. Jordan, Hannah T., et al. "Risk factors for persistence of lower respiratory symptoms among community members exposed to the 2001 World Trade Center terrorist attacks." *Occupational and Environmental Medicine* 74.6 (2017): 449-455.
8. Cohen, Mitchell D., et al. "Acute high-level exposure to WTC particles alters expression of genes associated with oxidative stress and immune function in the lung." *Journal of immunotoxicology* 12.2 (2015): 140-153.
9. Goldfarb, David G., et al. "Association of lung function decline with all-cause and cancer-cause mortality after World Trade Center dust exposure." *Annals of the American Thoracic Society* 20.8 (2023): 1136-1143.
10. Boffetta, Paolo, et al. "Cancer risk among World Trade Center rescue and recovery workers: a review." *CA: A Cancer Journal for Clinicians* 72.4 (2022): 308-314.
11. Durmus, Nedim, et al. "Characteristics of cancer patients in the world Trade center environmental health center." *International Journal of Environmental Research and Public Health* 17.19 (2020): 7190.
12. Celedón, J. C., et al. "Chronic Obstructive Pulmonary Disease in WTC Workers—Diagnoses and Transitions." (2022).
13. Weiden, M. D. "Treatment Response of WTC Related Airway Injury." (2023).
14. Cohen, Mitchell D., Lung-Chi Chen, and Morton Lippmann. "World Trade Center (WTC) dust." *Environmental Toxicants: Human Exposures and Their Health Effects* (2020): 973-997.
15. Weber, Jonathan, et al. "Quantitative CT evidence of airway inflammation in WTC workers and volunteers with low FVC spirometric pattern." *Lung* 198.3 (2020): 555-563.
16. Moline, Jacqueline, Leigh Wilson, and Francine R. Smith. "The Influence of the WTC Programs on Research." *World Trade Center Pulmonary Diseases and Multi-Organ System Manifestations*. Springer International Publishing, 2017. 1-19.
17. Jo, Eun-Jung, and Woo-Jung Song. "Environmental triggers for chronic cough." *Asia Pacific Allergy* 9.2 (2019): e16.
18. Gargano, Lisa M., et al. "Review of non-respiratory, non-cancer physical health conditions from exposure to the World Trade Center disaster." *International journal of environmental research and public health* 15.2 (2018): 253.



19. Smith, Erin, Lisa Holmes, and Brigid Larkin. "Health trends among 9/11 responders from 2011–2021: a review of World Trade Center Health Program statistics." *Prehospital and disaster medicine* 36.5 (2021): 621-626.
20. Calvert, Geoffrey M., et al. "The world trade center health program: an introduction to best practices." *Archives of environmental & occupational health* 78.4 (2023): 199-205.
21. Azofeifa, Alejandro. "World trade center health program—United States, 2012–2020." *MMWR. Surveillance Summaries* 70 (2021).
22. Santiago-Colón, Albeliz, et al. "World Trade Center health program: First decade of research." *International journal of environmental research and public health* 17.19 (2020): 7290.
23. Nolan, Anna, et al. "Inflammatory biomarkers predict airflow obstruction after exposure to World Trade Center dust." *Chest* 142.2 (2012): 412-418.
24. Levin, Stephen, et al. "Health effects of World Trade Center site workers." *American journal of industrial medicine* 42.6 (2002): 545-547.
25. Tao, Xuguang Grant, et al. "The world trade center clean up and recovery worker cohort study: respiratory health amongst cleanup workers approximately 20 months after initial exposure at the disaster site." *Journal of occupational and environmental medicine* 49.10 (2007): 1063-1072.
26. Wisnivesky, Juan P., et al. "Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study." *The Lancet* 378.9794 (2011): 888-897.
27. Liu, Xiaoxue, et al. "The effect of World Trade Center exposure on the timing of diagnoses of obstructive airway disease, chronic rhinosinusitis, and gastroesophageal reflux disease." *Frontiers in public health* 5 (2017): 2.
28. Lin, Shao, et al. "Lower respiratory symptoms among residents living near the World Trade Center, two and four years after 9/11." *International journal of occupational and environmental health* 16.1 (2010): 44-52.
29. Herbert, Robin, et al. "The World Trade Center disaster and the health of workers: five-year assessment of a unique medical screening program." *Environmental health perspectives* 114.12 (2006): 1853-1858.
30. de la Hoz, Rafael E., et al. "Reflux symptoms and disorders and pulmonary disease in former World Trade Center rescue and recovery workers and



- volunteers." *Journal of occupational and environmental medicine* 50.12 (2008): 1351-1354.
31. Aldrich, T. K., et al. "Cough and Bronchial Responsiveness in Firefighters at the World Trade Center Site." (2002).
32. de la Hoz, Rafael E. "Occupational asthma and lower airway disease among World Trade Center workers and volunteers." *Current allergy and asthma reports* 10.4 (2010): 287-294.
33. Reibman, Joan, et al. "Characteristics of a residential and working community with diverse exposure to World Trade Center dust, gas, and fumes." *Journal of Occupational and Environmental Medicine* 51.5 (2009): 534-541.
34. Webber, Mayris P., et al. "Trends in respiratory symptoms of firefighters exposed to the world trade center disaster: 2001–2005." *Environmental health perspectives* 117.6 (2009): 975-980.
35. Berger, Kenneth I., et al. "Lessons from the World Trade Center disaster: airway disease presenting as restrictive dysfunction." *Chest* 144.1 (2013): 249-257.
36. Reibman, Joan, et al. "The World Trade Center residents' respiratory health study: new-onset respiratory symptoms and pulmonary function." *Environmental health perspectives* 113.4 (2005): 406-411.
37. Herbstman, Julie B., et al. "Respiratory effects of inhalation exposure among workers during the clean-up effort at the World Trade Center disaster site." *Environmental research* 99.1 (2005): 85-92.
38. Rom, William N., et al. "Emerging exposures and respiratory health: World Trade Center dust." *Proceedings of the American Thoracic Society* 7.2 (2010): 142-145.
39. Landrigan, Philip J., et al. "Health and environmental consequences of the world trade center disaster." *Environmental health perspectives* 112.6 (2004): 731-739.
40. Niles, Justin K., et al. "Comorbid trends in World Trade Center cough syndrome and probable posttraumatic stress disorder in firefighters." *Chest* 140.5 (2011): 1146-1154.
41. Scanlon, Paul D. "World Trade Center cough—a lingering legacy and a cautionary tale." *New England Journal of Medicine* 347.11 (2002): 840-842.