9.11 World Trade Center Health Program

Evaluation of Scientific Evidence Supporting the Addition of Ischemic and Hemorrhagic Stroke to the List of WTC-Related Health Conditions

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I. EXECUTIVE SUMMARY

As directed by the Administrator of the World Trade Center (WTC) Health Program (Administrator), the WTC Health Program Science Team (Science Team) reviewed two petitions — **Petitions 048** and **051a** — requesting the addition of stroke, both ischemic and hemorrhagic, to the List of WTC-Related Health Conditions (the List). In related actions, the Administrator previously evaluated requests for "atherosclerosis" and "two forms of stroke, both ischemic and non-aneurysmal hemorrhagic," in **Petition 012**[1] and **Petition 020**,[2] respectively; both evaluations resulted in findings of *insufficient evidence* to add stroke to the List.

The Science Team evaluated the scientific evidence of a causal association between 9/11 exposures and stroke in accordance with the *Policy and Procedures for Adding Non-Cancer Health Conditions to the List of WTC-Related Health Conditions (Policy and Procedures)* [NIOSH 2026a]. A literature review of peer-reviewed, published, epidemiologic studies of stroke between September 2001 and July 2026 identified nine high-quality studies reporting on the risk of stroke in 9/11-exposed populations.

The Science Team evaluated the information from these nine high-quality studies identified in the review of the literature, including three studies identified in the previous literature reviews conducted for **Petition 012** and **Petition 020**, individually and together, to characterize the available scientific evidence of a causal association between 9/11 exposures and stroke. Based on the weight of evidence, the Science Team concludes that: (1) the available evidence of a causal association between 9/11 exposures and ischemic stroke is *limited* (Category III);[3] and (2) the available evidence of a causal association between 9/11 exposures and hemorrhagic stroke is inadequate (Category V).[4]

II. BACKGROUND

Pursuant to the James Zadroga 9/11 Health and Compensation Act of 2010,[5] an interested party may petition the Administrator of the WTC Health Program for the addition of a health condition to the List of conditions eligible for treatment in the Program.[6,7] To petition the Program, petitioners must submit, in writing, their name, contact information, and signature of the interested party requesting the addition of a health condition to the List; a statement of intent to petition for the addition of a health condition to the List; the name or description of the health condition; and reasons for adding the health condition to the List, including the medical basis for the association between the September 11, 2001, terrorist attacks and the condition.[8] These requirements are further explained in the *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions (Policy and Procedures for Handling Submissions and Petitions)* [NIOSH 2026b]. Submissions that meet all requirements are considered valid petitions.

1 *See* Federal Register, Vol. 81, No. 240, Wednesday, December 14, 2016, 90295-90297, https://www.govinfo.gov/content/pkg/FR-2016-12-14/pdf/2016-29816.pdf.
2 *See* Federal Register, Vol. 84, No. 37, Monday, February 25, 2019, 5972-5977, https://www.govinfo.gov/content/pkg/FR-2019-02-25/pdf/2019-02941.pdf.
3 *See Policy and Procedures*, Section V.C. [NIOSH 2026a].
4 *See Policy and Procedures*, Section V.E. [NIOSH 2026a].
5 Title I of Pub. L. 111-347, as amended by Pub. L. 114-113, Pub. L. 116-59, Pub. L. 117-328, Pub. L. 118-31, and Pub. L. 119-75; codified at 42 U.S.C. §§ 300mm – 300mm-64.
6 42 U.S.C. § 300mm-22(a)(6)(B).
7 The current List of WTC-Related Health Conditions is found in WTC Health Program regulations in Title 42 of the Code of Federal Regulations (CFR) Part 88 (42 C.F.R. § 88.15).
8 *See* 42 C.F.R. § 88.16(a)(1).

A. Petition 048

On September 3, 2023, the Administrator received a submission requesting the addition of "myocardial infraction [*sic*], unstable angina, obstructive coronary artery disease, ischemic cardiomyopathy, ischemic congestive heart failure, arrythmias (due to any of the above), stroke, and peripheral vascular disease" to the List. Upon review, the submission was found to be a valid petition. The Administrator exercised his discretion[9] to separate the scientific evaluation of the eight conditions provided in the submission into three separate Petitions and evaluations:[10] (1) "myocardial infraction [*sic*], unstable angina, obstructive coronary artery disease, ischemic cardiomyopathy, ischemic congestive heart failure, arrythmias (due to any of the above);" (2) "stroke;" and (3) "peripheral vascular disease" (PVD).[11]

The Administrator directed that Group (1) health conditions be evaluated under **Petition 047.**[12] The second health condition, stroke, is assessed in the current evaluation under a new ordinal number as **Petition 048**. The third health condition, PVD, will be evaluated in a separate evaluation under a new ordinal number as **Petition 048a**.

B. Petition 051a

On November 1, 2023, the Administrator received a submission requesting the addition of "cardiovascular diseases including coronary artery disease, myocardial infarction, stroke, congestive heart failure" to the List. Upon review, the submission was found to be valid for both cardiovascular diseases (CVD) and stroke. The Administrator exercised his discretion to separate the scientific evaluation of the conditions provided in the submission. The Administrator directed that those parts of the submission valid for CVD be evaluated as **Petition 051**,[13] and those parts valid for stroke be assigned an ordinal number and evaluated as **Petition 051a**.

C. Previous Petitions

The Administrator previously evaluated stroke for potential addition to the List. On April 11, 2016, the Administrator received two submissions, combined into **Petition 012**, to add "atherosclerosis" to the List — an antecedent health condition affecting the arteries that may lead to a stroke.[14] The Administrator's determination that the available evidence did not have the potential to provide a basis for a decision on whether to add atherosclerosis to the List was published in

9 *See Policy and Procedures for Handling Submissions and Petitions*, Section VII.C.2. [NIOSH 2026b]

10 To ensure a comprehensive scientific evaluation of each of the specific health conditions requested in the submission, each of which are associated with a large volume of peer-reviewed, published, scientific studies, the Administrator directed the Science Team to review the scientific evidence for the requested health conditions in three separate evaluations pertaining to conditions: (1) affecting oxygen supply to the heart (i.e., ischemia); (2) affecting blood supply to the brain (i.e., ischemic and hemorrhagic stroke); and (3) affecting the peripheral artery system. *See infra*, note 11.

11 The Administrator understands the term "peripheral vascular disease" to mean the health condition known as "peripheral artery disease." *See* Campia et al. [2019].

12 *See* https://www.cdc.gov/niosh/docket/archive/pdfs/niosh-094/2026-white-paper-eval-evidence-supporting-ischemic-v7rw-0622.pdf

13 *Ibid*.

14 The Administrator understands the term "stroke," also known as a cerebral vascular accident (CVA) or brain attack, to be a group of health conditions within a category called cerebrovascular diseases (CeVD) and to be a distinct subcategory of CVD. Stroke is generally described as a sudden onset of loss of focal neurological function caused by ischemia/infarction and/or hemorrhage in the relevant part of the brain, retina, or spinal cord. See Hankey [2017].

the *Federal Register* on December 14, 2016.[15]

On August 26, 2018, the Administrator received a submission requesting the addition of "two forms of stroke, both ischemic and non-aneurysmal hemorrhagic" to the List. The submission was found to be valid for stroke and evaluated as **Petition 020**. Following the Science Team's evaluation according to the *Policy and Procedures* [NIOSH 2017] in effect at the time, the Administrator published a finding of *insufficient evidence* to support adding ischemic or hemorrhagic stroke to the List on February 25, 2019.[16] The findings from these two previous evaluations are discussed in Sections VIII.B.1. and C.1. below.

III. PURPOSE

The purpose of this evaluation is to assess the scientific evidence from peer-reviewed, published, epidemiologic studies of stroke in the 9/11-exposed population[17] to determine whether sufficient evidence of a causal association between 9/11-related exposures, including exposure to 9/11 agents,[18] and the requested health condition exists to support adding the condition to the List. This evaluation is being provided to the Administrator to inform the Administrator's determination regarding **Petitions 048** and **051a** in accordance with the WTC Health Program's *Policy and Procedures* [NIOSH 2026a].

IV. REVIEW OF THE MEDICAL BASIS INFORMATION PROVIDED BY THE PETITIONERS

The validity of each petition was established by the Program in accordance with Program regulations and the *Policy and Procedures for Handling Submissions and Petitions* [NIOSH 2026b]. The Program examined the references provided with each submission to determine whether they included a medical basis for the association between the September 11, 2001, terrorist attacks and the health condition to be added to the List. *See* **Table 1a**. Across the two petitions, 10 distinct studies provided by the petitioners in support of their petitions were determined to be sufficient medical basis for initiating this evaluation. *See* **Table 1b**.

A. Petition 048

As noted above in Section II.A., **Petition 048** was separated from **Petition 047** and reviewed only for the health condition of stroke. **Petition 048** provided 33 studies as medical basis. These 33 studies covered several cardiovascular and cerebrovascular health conditions, including "MI, unstable angina, obstructive coronary artery disease, ischemic cardiomyopathy, ischemic congestive heart failure, arrythmias (due to any of the above), stroke, and [PVD]."

15 *See supra*, note 1.
16 *See supra*, note 2.
17 9/11-exposed population means those persons who can reasonably be assumed to have been exposed to hazards resulting from the September 11, 2001, terrorist attacks, including those 9/11 agents identified in the Program's *Development of the Inventory of 9/11 Agents (Inventory)*, within the geographic areas identified in the WTC Health Program's eligibility criteria; such populations may include, but are not limited to, WTC Health Program members. The Inventory includes a catalog of chemical, physical, biological, and other hazards that may have been present at the disaster areas. *See* NIOSH [2018].
18 9/11 agents are chemical, physical, biological, or other agents or hazards reported in a peer-reviewed, published exposure assessment study of responders, recovery workers, or survivors who were present in the New York City disaster area, or at the Pentagon site, or the Shanksville, Pennsylvania site, as those locations are defined in 42 C.F.R. § 88.1, as well as those hazards not identified in a peer-reviewed, published, exposure assessment study, but which are reasonably assumed to have been present at any of the three sites. Known 9/11 agents are established in the *Inventory* [NIOSH 2018].

Sufficient Medical Basis Studies. Ten of the 33 studies submitted with **Petition 048** provided sufficient medical basis for stroke [Brook et al. 2010; Newby et al. 2015; Cohen et al. 2017; Thurston et al. 2017; Cascio and Long 2018; Cohen et al. 2019; EPA 2019; Newman et al. 2020; Sloan et al. 2021; Yu et al. 2021].

Three of the 10 studies in **Petition 048** that provided sufficient medical basis [Cohen et al. 2019; Sloan et al. 2021; Yu et al. 2021] specifically examined CVD and/or stroke within the 9/11-exposed population. These three studies were also identified in the literature search and are further discussed in Section VIII.C.2.a., d., and e.

Cohen et al. [2019] is a peer-reviewed, published longitudinal cohort study designed to assess whether 9/11 exposures were associated with elevated CVD risk, including but not limited to myocardial infarction (MI), stroke, unstable angina, coronary artery surgery or angioplasty, congestive heart failure, CVD death, stable angina, and cardiomyopathy in Fire Department of New York (FDNY) firefighters. Positive associations were observed between CVD and 9/11 exposures related to time of arrival and length of response.

Sloan et al. [2021] is a peer-reviewed, published, prospective cohort study designed to examine the annual and cumulative incidence of CVD, including coronary artery disease (CAD), MI, stroke, and congestive heart failure, among the WTC Health Program General Responder Cohort (GRC); it reported increased CVD risk in males and females exposed to the WTC dust cloud compared to those that were not exposed to the dust cloud (i.e., arrived on or after September 12, 2001).

Yu et al. [2021] is a longitudinal study that examined the risk of stroke among WTC Health Registry (WTCHR) enrollees. The study found that WTC dust exposure is a possible risk factor for ischemic stroke but not for hemorrhagic stroke.

Seven of the 10 studies in **Petition 048** that provided sufficient medical basis [Brook et al. 2010; Newby et al. 2015; Cohen et al. 2017; Thurston et al. 2017; Cascio and Long 2018; EPA 2019; Newman et al. 2020] described increased stroke risks associated with air pollution exposure, including particulate matter (PM) with an aerodynamic diameter < 2.5 micrometers (μm) in diameter ($PM_{2.5}$), a 9/11 agent. These seven studies are briefly summarized below.

Brook et al. [2010] presented a scientific statement from the American Heart Association (AHA) concluding that the available evidence supports a causal relationship between exposure to $PM_{2.5}$ and increased stroke morbidity and mortality. The AHA further determined that $PM_{2.5}$ exposure should be regarded as a modifiable risk factor contributing to stroke and other cardiovascular-related deaths.

Newby et al. [2015] is a scientific review conducted by the European Society of Cardiology (ESC) evaluating the evidence linking air pollution (whose components include the 9/11 agents $PM_{2.5}$, PM with a nominal mean aerodynamic diameter less than or equal to 10 μm [PM_{10}], ozone, nitrogen dioxide [NO_2], volatile organic compounds [including benzene], carbon monoxide [CO], and sulfur dioxide [SO_2]), to stroke and other types of CVD, concluding that air pollution increases the risk of stroke morbidity and mortality. The ESC also outlined

potential biological mechanisms underlying this relationship and determined that air pollution should be considered a modifiable risk factor for types of CVD, including stroke.

Cohen et al. [2017] estimated global population-weighted mean $PM_{2.5}$ and ozone concentrations. It also explored global spatial and temporal trends in increased mortality and burden of disease, including increased stroke, attributable to $PM_{2.5}$. Ambient $PM_{2.5}$ was found to be the fifth-ranked risk factor for global deaths in 2015, and CVD (comprising ischemic heart disease [IHD] and cerebrovascular disease) accounted for most of those deaths. The authors described the potential for substantial health benefits from reduction of air pollution exposure.

Thurston et al. [2017] is a joint European Respiratory Society/American Thoracic Society policy statement to answer the question "what constitutes an adverse health effect of air pollution?" It provides an analytical framework on how to interpret scientific evidence on the health effects of air pollution for risk management purposes. The statement defines ischemic stroke as an adverse effect of air pollution. It also provides references to papers that describe increased risks for stroke from $PM_{2.5}$ exposure.

Cascio and Long [2018] provided a non-systematic review[19] on the CVD outcomes, including stroke, from air pollution. The review reported that $PM_{2.5}$ is associated with increased cerebrovascular events.

EPA [2019] is a detailed integrated science assessment that examined the impact of PM, including $PM_{2.5}$, on various CVD outcomes, including stroke. The assessment concluded that there is some evidence that long-term (1 month to years) exposure to $PM_{2.5}$ increases stroke risk.

Newman et al. [2020] is a Journal of the American College of Cardiology (JACC) state-of-the-art review of the cardiopulmonary impact of particulate air pollution in high-risk populations. It recognized that air pollution, including $PM_{2.5}$, poses stroke and other CVD risks. The authors proposed actions to reduce those stroke and CVD risks and suggested methods to study the effectiveness of those actions.

Insufficient Medical Basis Studies. A total of 23 studies submitted with **Petition 048** did not provide sufficient medical basis for stroke [Lioy et al. 2002; Wanahita et al. 2010; Jordan et al. 2011b; Jordan et al. 2013; Brackbill et al. 2014; Devlin et al. 2014; Beristianos et al. 2016; Kaufman et al. 2016; Shanley et al. 2016; Alper et al. 2017; Edmondson and von Kanel 2017; Yu et al. 2018; Ghio et al. 2018; Jordan et al. 2018; Remch et al. 2018; McGuinn et al. 2019; Ward-Caviness 2019; Jhun et al. 2019; Scherrer et al. 2020; O'Donnell et al. 2021; Serra et al. 2021; Hargrave et al. 2022; Li et al. 2023].

Of the 23 studies that did not provide sufficient medical basis in **Petition 048** for stroke, five were supportive of the biological plausibility for a causal relationship between post-traumatic stress disorder (PTSD) and IHD [Beristianos et al. 2016; Edmondson and von Kanel 2017; Scherrer et al. 2020; O'Donnell et al. 2021;

19 A systematic review collects and synthesizes all available, relevant evidence which brings together all existing primary studies for review and differs from other types of literature review in several major ways. Systematic review requires a transparent, reproducible methodology which indicates how studies were identified and the criteria upon which they were included or excluded. Systematic reviews provide methods for data extraction, data analysis, and quality assessment. In contrast, a non-systematic review does not provide a methodology that can be used to reproduce findings, nor inclusion and exclusion criteria, methods for data extraction, analysis, nor quality assessment. See Page et al. [2021].

Hargrave et al. 2022]. Two of the 23 studies were cross-sectional studies that evaluated the association between PM exposure and elevated serum lipids, potentially mediating air pollution-related effects on CVD [Shanley et al. 2016; McGuinn et al. 2019]. One of the 23 studies characterized the dust/smoke that settled in lower Manhattan after the collapse of the WTC on September 11, 2001, but did not examine any health conditions related to 9/11-exposures [Lioy et al. 2002]. One of the 23 studies provided a review of gene-air pollution interaction studies for CVD and provided possible mechanistic information on the association between PM exposure and CVD [Ward-Caviness 2019]. One of the 23 studies provided a review of environmental pollutant exposures associated with peripheral artery disease [Serra et al. 2021]. Three studies examined the CVD risks from environmental exposures not known to be 9/11 agents, including ultrafine particles (aerodynamic diameter < 0.1 μm), humic-like substances,[20] and black carbon [Devlin et al. 2014; Ghio et al. 2018; Jhun et al. 2019]. Two of the 23 studies examined coronary artery calcium scores, which are used to assess coronary atherosclerosis, but did not assess stroke [Wanahita et al. 2010; Kaufman et al. 2016]. Three of the 23 studies assessed certain CVD outcomes, but not stroke, in 9/11 exposed populations [Jordan et al. 2011b; Brackbill et al. 2014; Alper et al. 2017]. Two of the 23 studies assessed composite outcomes that included stroke but did not find a positive association between 9/11 exposures and those outcomes [Jordan et al. 2018; Li et al. 2023]. These two studies were identified in the literature search and are discussed in Section VIII.B.2.d., and e.

Finally, three of the 23 studies were not sufficient medical basis because they were included in the 2019 evaluation of **Petition 020** [Jordan et al. 2013; Remch et al. 2018; Yu et al. 2018].[21]

Jordan et al. [2013] is a longitudinal study of CVD and CeVD hospitalizations in a cohort of WTCHR enrollees residing in New York State. The study found that male enrollees who had PTSD at study enrollment (between September 12, 2003, and November 24, 2004) had an increased risk for CeVD hospitalization while risk for CeVD hospitalization among female enrollees who had PTSD at study enrollment was non-significantly elevated. Remch et al. [2018] is a peer-reviewed, published longitudinal study of WTC Health Program members who were first responders on or after September 11, 2001, examining whether PTSD is a risk factor for MI and stroke combined. The study reported hazard ratios (HRs) for several 9/11 exposure measures and the MI/stroke outcome. Some of the HRs were increased and some were not, but none were statistically significant after adjustment for the presence of PTSD. Yu et al. [2018] conducted a cohort study to investigate the risk of stroke among WTC responders and survivors who experienced PTSD and who had intense exposure to WTC dust. The study found that WTC dust cloud exposure was independently associated with an increased risk for stroke among WTC responders and survivors. These three studies were found in the literature search and are discussed in Section VIII.C.1.

B. Petition 051a

Petition 051a provided four studies as medical basis [Remch et al. 2018; Cohen et

20 Humic substances are derived from degraded plant remains and are an important source of organic matter. *See* Tiwari et al. [2023].

21 *See supra*, note 2.

al. 2019; Berry and Duncker 2020; Sloan et al. 2021]. Cohen et al. [2019] and Sloan et al. [2021] provided sufficient medical basis and are described under **Petition 048** above; they are further discussed in Section VIII.C.2.a. and d., respectively.

Remch et al. [2018], was previously evaluated in **Petition 020** and therefore was found not to provide sufficient medical basis.[22] Remch et al. [2018] is described under **Petition 048** above and is further discussed in Section VIII.C.1.b.

Barry and Duncker [2020] is a commentary on coronary microvascular disease (also called small artery disease or small vessel disease) as a potential contributing cause of IHD [Berry and Duncker 2020]. This commentary did not provide any medical basis information related to stroke and was not considered further.

V. EVALUATED HEALTH CONDITION

In accordance with the *Policy and Procedures* [NIOSH 2026a], the Science Team reviewed the information provided by the petitioners and determined that the health condition of interest for this evaluation was stroke (International Statistical Classification of Diseases and Related Health Problems [ICD] 10 codes I60, I61, I63, I64, and G45).

The term "stroke," also known as CVA or "brain attack," is a group of health conditions within the category of CeVD. Stroke is generally described as a sudden onset of loss of focal neurological function caused by infarction or hemorrhage in the relevant part of the brain, retina, or spinal cord [Hankey 2017]. In 2023, stroke ranked fourth in the United States among all causes of death, behind diseases of the heart, cancer, and unintentional injuries/accidents [Tejada-Vera et al. 2025]. Stroke accounts for 2–4% of total health-care costs and, in industrialized countries, accounts for more than 4% of direct health-care costs [Donnan et al. 2008]. Globally, stroke is the third leading cause of disability-adjusted life years [Diseases and Injuries 2020]. According to recent statistics published by the AHA, the prevalence of stroke in the United States among those > 20 years of age is 3.3%, with about 795,000 new cases and 162,639 deaths occurring in 2023, at a cost of $49 billion [Palaniappan et al. 2026]. Stroke prevalence increases with advancing age, reaching 11% among those aged 80 years or more [Palaniappan et al. 2026]. In the United States, the lifetime risk of developing stroke is estimated to be 23% to 28.9% [GBD 2016 Lifetime Risk of Stroke Collaborators 2018].

Stroke is classified as ischemic or hemorrhagic. Based on recent AHA estimates, 87% of all strokes are ischemic (e.g., cerebral infarction, ICD 10 code I63), with about 10% subcategorized as intracerebral hemorrhagic (ICD 10 code I61), and roughly 3% subcategorized as subarachnoid hemorrhagic (ICD 10 code I60) [Palaniappan et al. 2026].

Hemorrhagic stroke generally occurs from a rupture of a blood vessel or an abnormal vascular structure. About two-thirds of patients with primary cerebral hemorrhage have pre-existing or newly diagnosed hypertension [Donnan et al. 2008]. Subarachnoid hemorrhage refers to bleeding into the cerebrospinal fluid within the subarachnoid space that surrounds the brain. Ischemic stroke is a disruption of normal blood flow to a part of the brain, usually from transient or permanent blood vessel blockage, that results in sudden loss of neurologic function. There are three subtypes of brain ischemia that cause ischemic stroke: (1) *thrombosis* (i.e., local *in situ* obstruction of an artery which can arise from disease

22 *See supra*, note 2.

of the arterial wall [e.g., arteriosclerosis], dissection [i.e., a tear in one or more layers of a blood vessel wall], or fibromuscular dysplasia [nonatherosclerotic, noninflammatory vascular disease that may result in arterial stenosis, occlusion, aneurysm, or dissection]) [Olin et al. 2014]; (2) *embolism* (i.e., particles of debris that originate elsewhere that block arterial access to a particular brain region); and (3) *systemic hypoperfusion* (i.e., a condition where the body's organs and tissues receive insufficient blood flow, leading to oxygen deprivation and potential multi-organ failure) [Klijn and Kappelle 2010]. A transient ischemic attack (TIA, ICD 10 code G45) is a type of ischemic stroke with focal dysfunction lasting less than 24 hours in duration and with no imaging evidence of infarction (i.e., obstruction of blood supply to brain tissue) [Hankey et al. 2017].

Petitions 048 and **051a** requested the addition of stroke, including both ischemic and hemorrhagic types. Of the 10 studies that provided sufficient medical basis, four distinguish between the two types of stroke and provide sufficient medical basis for both ischemic and hemorrhagic stroke [Brook et al. 2010; Newby et al. 2015; EPA 2019; Yu et al. 2021]. The other six studies do not distinguish between the two types of stroke [Cohen et al. 2017; Casio and Long 2018; Thurston et al. 2017; Cohen et al. 2019; Newman et al. 2020; Sloan et al. 2021]. The Administrator determined that the evaluation of scientific evidence should address both ischemic and hemorrhagic stroke.

VI. RISK FACTORS FOR THE EVALUATED HEALTH CONDITION

A. General Risk Factors

Stroke risk factors, many of which are shared by both ischemic and hemorrhagic stroke [GBD 2019 Stroke Collaborators 2021; Gross et al. 2019], are classified into those that are modifiable and those that are non-modifiable. Among non-modifiable risk factors, age is a strong determinant of stroke, with a doubling of risk every decade above age 55 years [Donkor 2018]. In addition to age, important non-modifiable risk factors for stroke include family history of stroke, male sex, and Hispanic or Black race. As for modifiable risk factors, the AHA recently reported that about 87% of stroke was attributable to factors such as hypertension, obesity, hyperglycemia, hyperlipidemia, renal dysfunction, smoking, sedentary lifestyle, and an unhealthy diet [Palaniappan et al. 2026]. Hypertension is the leading contributor to death/disability for both ischemic and hemorrhagic stroke. As with cardiovascular endpoints, there is some evidence of an association between exposure to outdoor air pollution and stroke [Shah et al. 2015]. However, when compared with acute cardiac events, the relationship between air pollution and stroke is less clear.

Embolic causes of ischemic stroke include atrial fibrillation, atrial flutter, left atrial or left ventricular thrombus, presence of a mechanical heart valve, MI within the past month, history of MI with ejection fraction < 28%, and dilated cardiomyopathy [Caplan 1993]. Although these cardiac sources of emboli are risk factors for ischemic stroke, the treatment to prevent emboli involves anticoagulant therapy. Use of anticoagulants increases the risk of hemorrhage, including intracranial hemorrhage (i.e., hemorrhagic stroke) [McGrath et al. 2012]. Therefore, emboli can cause ischemic stroke, and the prevention of emboli can cause hemorrhagic stroke. However, antithrombotic therapy and anticoagulation provide a favorable risk-benefit ratio across most clinical scenarios involving

thromboembolism prevention and treatment, with the strongest net benefit seen in patients at moderate-to-high thromboembolic risk and without major bleeding risk factors [Diener and Hankey 2020].

Hemorrhagic stroke is characterized by spontaneous intraparenchymal hemorrhage (IPH). IPH is classified as primary or secondary [Gross et al. 2019]. Primary IPH refers to rupture of damaged small arteries or arterioles, most commonly secondary to either hypertension or cerebral amyloid angiopathy (CAA). CAA arises from β-amyloid deposition in cortical blood vessels; the vessels are consequently weakened and have an increased tendency to rupture, making CAA an independent risk factor for IPH. Secondary IPH can result from coagulopathy, vascular malformation rupture, cerebral venous thrombosis, mycotic aneurysm rupture, moyamoya, tumor, hemorrhagic conversion of an ischemic stroke, or vasculitis [Gross et al. 2019].

Excluding trauma, subarachnoid hemorrhage is caused by the rupture of an intracranial aneurysm in 80% of cases, while other causes include vascular malformations and vasculitis [Lawton and Vates 2017]. Patients with subarachnoid hemorrhage are younger than those affected by other stroke subtypes.

Mental health factors, including chronic stress (e.g., PTSD), depression, anxiety, and substance use disorder have been linked to stroke [Benjamin et al. 2019]. The precise mechanism by which mental disorders increase stroke risk remains uncertain [Visseren et al. 2021]. However, chronic stress triggers the release of stress hormones like cortisol and epinephrine, which can lead to increased heart rate, hypertension, and endothelial dysfunction. Additionally, poor mental health can lead to unhealthy behaviors such as smoking, unhealthy diet, and physical inactivity, further exacerbating stroke risk [Visseren et al. 2021].

B. 9/11 Risk Factors

The Science Team considered that among hazards listed in the *Inventory* [NIOSH 2018], the 9/11 exposures of greatest concern as possibly causal for stroke are PM inhalation and, to a lesser degree, neurotoxic chemicals (e.g., polycyclic aromatic hydrocarbons, metals). Exposure sources include the dense plume of dust, gases, and smoke caused by building collapse, burning jet fuel and building fires, as well as resuspension of contaminants during months of clean-up and recovery.

WTC PM consists of an alkaline (pH 9.0 to 11.0) mixture of pulverized cement, glass fibers, asbestos, neurotoxic metals (e.g., lead, cadmium, arsenic, and chromium), polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polychlorinated furans and dioxins in a matrix comprising mostly coarse particles, with more than 95% of the mass arising from PM > 10 µm in diameter [Lioy et al. 2002; Litten et al. 2003; Rayne et al. 2005]. Settled dust contained non-fibrous materials (e.g., cement) ranging between 47% to 50% by mass depending on sample location and about 40% glass fiber [Lioy et al. 2002]. Persons within the plume likely had short-term exposure to both $PM_{2.5}$ and coarse inhalable particles that exceeded 1,000 µg/m^3 [Lippmann et al. 2015]. Persons working in subsequent rescue and recovery operations were likely exposed to PM over months of clean-up activities (i.e., long-term exposure). Personal and

area monitoring during cleanup and recovery activities show elevated levels of respirable dust and silica ranging between 4.2 and 1,800 µg/m^3 [Pavilonis and Mirer 2017].

The U.S. Environmental Protection Agency (EPA) previously evaluated the evidence of associations between PM exposures and human health conditions, publishing its findings in its *Integrated Science Assessment (ISA) for Particulate Matter* [EPA 2019]. Details on the framework for the evaluation are described elsewhere [EPA 2015]. Exposure duration was categorized as either short-term (hours up to 1 month) or long-term (1 month to years) [EPA 2019, page P-14]. Based on the weight of evidence, EPA concluded that there is *a causal relationship* between short- and long-term exposure to $PM_{2.5}$ and cardiovascular effects, including stroke [EPA 2019, Sections 6.1 and 6.2].

The EPA further concluded that the evidence was only suggestive of, but not sufficient to, infer causal relationships between short- and long-term $PM_{10-2.5}$ (PM with normal mean aerodynamic diameter > 2.5 µm and < 10 µm) exposure or short-term exposure to ultrafine particles and cardiovascular effects, including stroke. The evidence of cardiovascular effects from long-term exposure to ultrafine particles was inadequate to make a causal determination.

A systematic review and meta-analysis found that exposure to lead and cadmium were separately associated with a significantly increased risk of stroke [Chowdhury et al. 2018]. The studies included in the meta-analysis involved those conducted in general populations, with levels of metals exposure ranging from low to moderate. They did not include effects of acute poisoning from those metals. Lead and cadmium are 9/11 agents.

The Science Team also looked at the confounding, modifying, or mediating effects of PTSD on the causal association between 9/11 exposure and stroke. However, PTSD itself is not considered a 9/11 exposure; therefore, studies that only examined the association between PTSD and CVD outcomes, including stroke, in the 9/11 population (e.g., Giesinger et al. [2020]) cannot provide evidence in support of a causal association between 9/11 exposures and stroke.

VII. SCIENTIFIC EVALUATION APPROACH

The Science Team evaluation was carried out in accordance with the *Policy and Procedures* [NIOSH 2026a] and includes the following steps: (1) develop a literature search protocol and conduct a search for peer-reviewed, published, epidemiologic studies of the health condition being evaluated among 9/11-exposed populations;[23] (2) review identified studies to determine which studies are high-quality studies for further evaluation;[24] (3) evaluate and integrate the evidence of a causal association between 9/11 exposures and the health condition being evaluated;[25] and (4) synthesize and interpret all findings to categorize the weight of evidence of a causal association between 9/11 exposures and the health condition evaluated.[26] The Science Team then advises the Administrator of its findings.[27]

23 *See Policy and Procedures*, Section III.B. [NIOSH 2026a].
24 *See Policy and Procedures*, Section III.C. [NIOSH 2026a].
25 *See Policy and Procedures*, Section IV. [NIOSH 2026a].
26 *See Policy and Procedures*, Section V. [NIOSH 2026a].
27 *See Policy and Procedures*, Section VI. [NIOSH 2026a].

VIII. REVIEW OF THE LITERATURE

A. Literature Search

The literature search identifies high-quality peer-reviewed, published, epidemiologic studies that provide evidence on the proposed causal association between 9/11 exposures and stroke. To identify potentially relevant studies, the Science Team searched abstracts and titles from peer-reviewed English language literature. The search of the English literature was broad and, in addition to terms used to identify epidemiologic studies of the 9/11-exposed population, search terms[28] used to uncover potentially informative studies included: cardiovascular disease, myocardial infarction (MI, acute MI), acute coronary syndrome, coronary thrombosis, stroke (cerebrovascular accident, transient ischemic attack, intracerebral hemorrhage, cerebral hemorrhage, subarachnoid hemorrhage, brain ischemia, brain infarction, cerebral infarction), angina (unstable angina, stable angina), angina pectoris, coronary occlusion, coronary artery obstruction, ischemia/reperfusion injury, reperfusion injury, myocardial ischemia, acute cardiac disease, coronary artery stenoses, coronary artery disease, ischemic heart disease, arterial stenosis, coronary artery surgery, coronary bypass surgery, coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), percutaneous intervention, angioplasty, coronary revascularization, myocardial revascularization, coronary artery revascularization, stent placement AND (heart or coronary or artery), coronary artery stenting, drug-eluting stent, carotid artery surgery, surgical revascularization, surgical bypass, aortic aneurysm, arterial aneurysm, arterial dissection, aortic dissection, peripheral arterial vascular intervention, peripheral artery disease, atherosclerotic disease, arteriosclerotic disease, peripheral artery occlusive disease, arterial syndrome, embolism, aortoiliac disease, femoropopliteal disease, and ischemic cardiomyopathy. A subsequent full search was conducted that included additional terms in recognition of new information obtained from the more recent petitions. The new terms were: brain aneurysm, intracranial aneurysm, cerebral aneurysm, saccular aneurysm, berry aneurysm, intracranial hemorrhage, varicose veins, venous thromboembolism, pulmonary embolism, deep vein thrombosis, VTE, DVT, thrombosis, venous thrombosis, vein thrombosis, venous disease, chronic venous disease, chronic venous insufficiency, venous leg ulcer, venous ulcer, venous ulceration, venous incompetence, venous stasis, varicose disease, coronary artery spasm, coronary spasm, prinzmetal angina, microvascular angina, MVA, vasospastic angina, spastic angina, coronary vasospasm, variant angina, anginal attack, coronary microvascular obstruction, coronary microvascular dysfunction, cardiac syndrome X, syndrome X, INOCA (ischemia with non-obstructive coronary artery disease), MINOCA (myocardial infarction with no obstructive coronary atherosclerosis), ischemic congestive heart failure, heart failure, arrythmias, ventricular, arrhythmia(s), cardiac arrest, ventricular fibrillation, ventricular tachycardia, sudden cardiac death, sudden death, atrial fibrillation, atrial flutter, tachyarrhythmia(s), tachycardia, supraventricular tachycardia, cardiac ectopy, ectopy, atrioventricular block, AV block, bundle branch block, heart block, cardiac conduction disease, and

28 The list of search terms provided coverage for both cardiovascular and cerebrovascular outcomes, although this evaluation was restricted to stroke. Literature providing evidence on cardiovascular outcomes only was used in a separate evaluation for ischemic heart disease. *See* https://www.cdc.gov/niosh/docket/archive/pdfs/niosh-094/2026-white-paper-eval-evidence-supporting-ischemic-v7rw-0622.pdf.

cardiac conduction defect. Both searches were conducted among the following databases: APA PsycInfo®, CINAHL (EBSCOhost), Embase Classic+Embase, Health & Safety Science Abstracts (ProQuest), NIOSHTIC-2, Ovid MEDLINE®, Scopus, and Toxicology Abstracts (ProQuest).

Following the baseline search, additional weekly searches were conducted using the WTC Health Program Bibliographic Database, a database of relevant WTC-related research maintained by the Program and updated at least weekly using a standing search of the previously mentioned databases. The last follow-up search was conducted in June 2026. This two-pronged approach ensures all relevant and up-to-date literature is available for the evaluation.

The literature search identified 18 peer-reviewed, published, epidemiologic studies of stroke in 9/11-exposed populations for full review as potential studies for evaluation [Brackbill et al. 2006; Jordan et al. 2011a; Jordan et al. 2013; Mani et al. 2013; Stein et al. 2016; Wilkenfeld et al. 2016; Jordan et al. 2018; Remch et al. 2018; Yu et al. 2018; Cohen et al. 2019; Colbeth et al. 2020; Alper et al. 2021; Sloan et al. 2021; Yu et al. 2021; Li et al. 2023; Singh et al. 2023; Mueller et al. 2024; Parvin et al. 2026].

One of the 18 studies was reviewed in the 2016 evaluation of **Petition 012** and was reexamined in this evaluation [Mani et al. 2013]. It was determined not to demonstrate sufficient validity indicators to be further evaluated as a high-quality study. This study was removed from further consideration but is discussed in Section VIII.B.1.b. for completeness. *See* **Table 2**.

Four of the 18 studies were reviewed in the 2019 evaluation of **Petition 020** and were reexamined in this evaluation [Brackbill et al. 2006; Jordan et al. 2013; Yu et al. 2018; Remch et al. 2018].[29] *See* **Table 2**. Three of those four studies are considered high quality [Jordan et al. 2013; Yu et al. 2018; Remch et al. 2018] and are discussed in Section VIII.C.1. The fourth study [Brackbill et al. 2006] was removed from further consideration because it was a cross-sectional study whose findings were considered preliminary by its authors and because more recent longitudinal studies with larger sample sizes are available from the same cohort [Yu et al. 2018; Yu et al. 2021]. However, for the sake of completeness, Brackbill et al. [2006] is discussed in Section VIII.B.1.a.

Seven of the 18 studies identified in the literature were determined not to demonstrate sufficient validity indicators to be further evaluated as high-quality studies [Jordan et al. 2011a; Stein et al. 2016; Wilkenfeld et al. 2016; Jordan et al. 2018; Li et al. 2023; Singh et al. 2023; Parvin et al. 2026]. Three of these seven studies were published before the 2019 evaluation of **Petition 020** but were not reviewed as part of that evaluation [Jordan et al. 2011a; Stein et al. 2016; Jordan et al. 2018]. All seven studies were removed from further consideration but are discussed in Section VIII.B.2. for completeness.

The Science Team determined that the remaining six of the 18 identified studies [Cohen et al. 2019; Colbeth et al. 2020; Sloan et al. 2021; Yu et al. 2021; Alper et al. 2021; Mueller et al. 2024] had sufficient validity indicators to meet the standard for high-quality studies; these studies were not included in the previous evaluations of **Petitions 012** and **020**.[30] The review and evaluation of these six high-quality studies is included in Section VIII.C.2. *See* **Table 3**.

29 *See supra*, note 2.
30 *See Policy and Procedures*, Section III.C. [NIOSH 2026a].

B. Studies Removed from Further Consideration

1. Previously Reviewed Studies Removed from Further Consideration

Two previously reviewed studies that were identified in the literature search were determined by the Science Team not to demonstrate sufficient validity indicators and were removed from further consideration [Brackbill et al. 2006; Mani et al. 2013]. One of these studies [Mani et al. 2013] was reviewed in the 2016 evaluation of **Petition 012**. The other study [Brackbill et al. 2006] was previously reviewed in the 2019 evaluation of **Petition 020**. *See* **Table 2**. The findings from these two studies and their notable limitations were discussed in the published decisions on **Petitions 012**[31] and **020**.[32] They are also summarized below for completeness.

a. Brackbill et al. [2006]

Brackbill et al. [2006] conducted cross-sectional surveillance of self-reported cardiovascular health conditions among WTCHR enrollees (n = 8,418) aged ≥ 18 years at the time of the Wave 1 survey (2003–2004). These WTCHR participants were office workers and visitors present in any one of 38 collapsed or damaged buildings during the time between the first tower (WTC-2) impact and noon on 9/11, excluding those who were involved in rescue and recovery. Three proxy[33] exposure metrics were used separately to characterize 9/11 exposures: (1) being caught in the dust and debris cloud (yes/no); (2) the time of evacuation (before/after first tower collapsed); and (3) type of occupied building (collapsed/damaged). Stroke was determined by self-report of diagnosis by a healthcare professional. All models for self-reported stroke were adjusted for recruitment mode and sex.

Of an estimated 62,092 building occupants, 8,418 adult WTCHR enrollees were recruited for this study. Of these, 56% resided in New York City (NYC) on September 11, 2001, 27% were from New Jersey, and 14% were from New York State outside of NYC. About 61% of study participants occupied collapsed buildings before evacuation. The study group was mostly male (54%), and most participants (56%) were aged 25–44 years on September 11, 2001. Most participants (59.0%) were never-smokers. About 62% of participants were caught in the dust and debris cloud, and about 64% experienced three or more events that could potentially cause psychological trauma. The odds of reporting a stroke (OR = 5.6; 95% CI: 1.3, 24.4; n = 20) were increased among persons in the dust cloud compared with those without dust cloud exposure; however, confidence intervals were very wide. Analyses using alternative exposure indices provided little evidence of association.

The study by Brackbill et al. [2006] has notable weaknesses. First, most participants were self-identified and represent a small

31 *See supra*, note 1.
32 *See supra*, note 2
33 A proxy variable (measurement) is one that is used in place of a variable that cannot be directly measured. *See* Nilsson et al. [2023].

fraction (16.7%) of the exposed population. Biases from limitations in recruitment were not examined. Second, exposure and outcome data were self-reported without follow-up confirmation. Exposure was based on a single yes/no question regarding presence in the dust and debris cloud, but with no information on how the respondent interpreted being in the dust cloud. The survey was conducted 2 to 3 years after September 11, 2001, which may have affected recall. Reports on the validity of self-reported information on exposure and outcome within the 9/11-exposed population were not available. Third, the study is cross-sectional. Other than the self-reported condition and whether the diagnosis was pre- or post-September 11, 2001, there was no information on severity onset, or persistence of conditions. Fourth, information on other exposures (before and after 9/11), risk factors (e.g., smoking, diet, exercise, family history), or comorbid conditions (e.g., obesity, hypertension) that may have contributed to stroke risk was not available or was not considered. For example, models examining stroke did not control for age, race/ethnicity, and level of serious psychological distress (among other potential risk factors) due to small numbers. Fifth, inclusion of model covariates was limited because of the small sample size for stroke (n = 20).

Given the small sample size for stroke and cross-sectional design, the authors considered these findings preliminary, and the Science Team concurred. Furthermore, more recent longitudinal studies with larger sample sizes are available from the same cohort [Yu et al. 2018; Yu et al. 2021]. Brackbill et al. [2006] was not classified as among the most informative studies for this evaluation.

b. Mani et al. [2013]

Mani et al. [2013] described a cross-sectional pilot study exploring the feasibility of using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) to evaluate differences in atherosclerosis profiles in WTC responders exposed to high levels (arrived at "Ground Zero" during the morning of September 11, 2001, and were present during the collapse of one or both towers and the associated dust cloud) versus low levels (exposed on or after September 13, 2001) of WTC dust exposure. The study was a convenience sample of 31 law enforcement personnel (19 with self-reported high exposures and 12 with self-reported low exposures). The sample was recruited from the Law Enforcement Cardiovascular Screening Program (LECS) subset of the WTC Medical Monitoring and Treatment Program (MMTP), a precursor of the WTC Health Program for responders. The bilateral carotid arteries of all subjects were imaged with both multi-contrast MRI and DCE-MRI.[34] For DCE-MRI, the area under the curve (AUC) was calculated at 2 and 7 minutes after contrast agent injection. Ankle-

34 Multi-contrast MRI uses multiple different MRI sequences acquired at different time points to characterize plaque components based on their inherent tissue properties, typically without contrast administration. DCE-MRI involves rapid, serial imaging over time (typically 5–10 minutes) after injection of a single bolus of contrast to measure signal intensity changes and quantify plaque neovascularization through pharmacokinetic modeling. *See* Saba et al. [2018].

brachial index (ABI) measures (left and right) were also obtained.[35]

Participants were primarily male (90%), mean age was 45 years, and those with high WTC dust exposure were more likely to be smokers (current smokers: high WTC dust exposure = 5%; low WTC dust exposure = 0%. Former smokers: high WTC dust exposure = 16%; low WTC dust exposure = 8%). There were no significant differences in multi contrast MRI results between exposure groups. None of the participants in either exposure group had complex carotid artery plaques that could be classified. However, compared with those with low WTC dust exposure, those with high WTC dust exposure had significantly higher DCE-MRI AUC uptake (increased neovascularization) (AUC at 7 minutes: 2.65 ± 0.63 for high WTC dust exposure vs. 1.88 ± 0.69 for low WTC dust exposure, $p = 0.016$). The authors reported that fitting a multivariable regression model indicated that high WTC dust exposure, total cholesterol, and C-reactive protein levels were independent predictors of DCE-MRI AUC uptake (i.e., increased neovascularization); however, parameter estimates were not shown. Higher DCE-MRI AUC uptake may be a marker of increased progression of atherosclerosis. The authors also found that those with high WTC dust exposure had significantly lower mean right-sided ABI (high WTC dust exposure: ABI = 1.18 ± 0.08; low WTC dust exposure: ABI = 1.26 ± 0.08; $p = 0.017$). These mean ABI measures were within the normal range. ABI measures on the left side were not associated with WTC dust exposure.

Mani et al. [2013] has several limitations. The sample size was small and not representative of all 9/11-exposed groups since the study included only law enforcement responders. The authors did not report when the study was conducted and the interval between 9/11 exposure and data collection could not be determined. Detailed ABI methodology was not reported (e.g., whether the highest or lowest low extremity systolic pressures were used). Variables used to adjust findings were not reported. As such, although those with high WTC dust exposure were more likely to be smokers, it was not clear if findings were adjusted for smoking. The Science Team concurred with the study authors that these results are preliminary. Mani et al. [2013] was not classified as a high-quality study for this evaluation and is not discussed in Section IX.C.

2. Newly Identified Studies Removed from Further Consideration

Seven of the 18 studies identified in the literature search were determined not to demonstrate sufficient validity indicators to be further evaluated as high-quality studies [Jordan et al. 2011a; Stein et al. 2016; Wilkenfeld et al. 2016;

35 The ABI is a ratio of systolic blood pressure in the ankle to systolic pressure in the brachial arteries (i.e., the artery in the upper arm), assessed with Doppler ultrasonography. At the ankle, the dorsalis pedis or posterior tibial systolic pressure is used, generally whichever is higher, because the higher pressure may reflect best leg perfusion. However, using the lower of the dorsalis pedis and posterior tibial artery pressures for ABI calculation is more sensitive for detecting peripheral artery disease. In those without atherosclerotic obstruction, systolic pressures increase with greater distance from the heart, yielding higher systolic pressures at the ankle than at the brachial artery. Therefore, a normal ABI ranges from more than 1.00 to 1.40. Borderline low ABI is 0.91–0.99, and abnormal ABI is defined as < 0.90. ABI is separately measured on the right and left sides of the body. *See* Aboyans et al. [2012].

Jordan et al. 2018; Li et al. 2023; Singh et al. 2023; Parvin et al. 2026].

Five of these seven studies were excluded because they conducted external comparisons that were particularly vulnerable to strong selection bias given large differences between the 9/11-exposed population and the reference populations in all five studies [Jordan et al. 2011a; Stein et al. 2016; Jordan et al. 2018; Li et al. 2023; Singh et al. 2023]. The external reference population varied by study and was the general population of NYC in two studies [Jordan et al. 2011a; Jordan et al. 2018], the general population of New York State in one study [Li et al. 2023], and the U.S. general population in four studies [Stein et al. 2016; Jordan et al. 2018; Li et al. 2023; Singh et al. 2023].[36] Selection bias would tend to cause underestimation of stroke risks. Cause of death information from death certificates by linkages to the CDC National Death Index (NDI)[37] and NYC vital records likely led to death undercounting. In addition, the health condition examined by all five studies was not stroke and instead was NIOSH Life Table Analysis System (LTAS) Major 17 (other diseases of the circulatory system).[38] This is a composite outcome that included CeVD; hypertension without heart disease; and diseases of the arteries, veins, and lymphatic vessels, including pulmonary embolism, aortic aneurysm, pulmonary hypertension, peripheral artery disease, thrombophlebitis, and esophageal varices [Robinson et al. 2006; Schubauer-Berigan et al. 2011]. Findings from analyses using composite outcomes are largely uncertain and merit cautious interpretation in causal inference. None of these five studies reported internal analyses examining the exposure-response association among cohort members for stroke mortality and none of the studies provided any evidence of an association between 9/11-exposures and Major 17. In contrast, the high-quality studies summarized in Section VIII.C. used more appropriate reference populations (e.g., comparing those who experienced high levels of WTC exposures to those who experienced low levels of WTC exposures) and/or used health condition outcomes more specific to stroke.[39]

The sixth study, Parvin et al. [2016], was excluded by the Science Team because it did not examine the association between 9/11-exposures and any CVD outcomes. Instead, it compared the mortality experience of responders enrolled in the WTC Health Program compared to responders who were not enrolled (i.e., WTCHR enrollees). Parvin et al. [2026] found lower mortality among WTC Health Program-enrolled responders.

The seventh study, Wilkenfeld et al. [2016], is a cross-sectional survey that compared the frequency of neuropathic symptoms and medical comorbidities, such as stroke, among a convenience sample of WTC-exposed and non-WTC-exposed respondents. Wilkenfeld et al. [2016] did not find a difference in the frequency of stroke among the comparison groups. The study did not evaluate the strength of association between 9/11 exposures and stroke, but only the

36 Note that the Jordan et al. [2018] and Li et al. [2023] mortality studies used two different external reference populations.
37 NDI is a resource to help researchers find out if participants in their studies have died. NDI also can help researchers learn selected mortality information for study participants' deaths. NDI provides the public health and medical research community a single source for obtaining selected mortality data from death certificates for approved uses. *See* https://www.cdc.gov/nchs/ndi/.
38 LTAS software package was used in several studies in this evaluation. LTAS support was discontinued in 2022, but its functionality was retained in software available on another platform. *See* Bertke et al. [2022].
39 *See Policy and Procedures*, Section IV.A.1. footnote 28 [NIOSH 2026a].

existence of an association. The study had other limitations that prevented the Science Team from considering it further.

Each of these seven excluded studies is briefly described below.

a. Jordan et al. [2011a]

Jordan et al. [2011a] examined mortality in a cohort study of WTCHR enrollees followed between 2003 and 2009. The cohort comprised both rescue/recovery workers (*n* = 13,337; 74,967 person-years) and community members (*n* = 28,593; 161,519 person-years), the latter consisting of residents, workers, school students and staff, and passers-by. However, unlike the subsequent mortality study [Jordan et al. 2018], participants in this study were restricted to persons residing in NYC at the time of enrollment. Information about WTC exposures was derived from WTCHR Wave 1 (2003–2004) questionnaire data. In general, exposure was classified as high, intermediate, or low using different classification schemes for rescue/recovery workers and community members, as well as for the full cohort (restricted to high vs. low). The underlying causes of death were identified primarily via linkage to NYC vital records. The CDC NDI was used only to identify deaths among NYC residents that occurred outside of NYC. Deaths were grouped according to the NIOSH LTAS [Robinson et al. 2006; Schubauer-Berigan et al. 2011].

The study outcome was NIOSH LTAS Major 17 (other diseases of the circulatory system). Only external comparisons were reported. Standardized mortality ratios (SMRs) accounting for age, sex, race/ethnicity, and calendar period were calculated for all participants and stratified by enrollment, with U.S. population rates referent.

There were 44 deaths from Major 17 among participants in the Jordan et al. [2011a] study. Mortality from Major 17 was significantly decreased in all participants (SMR = 0.54; 95% CI: 0.39, 0.72), in rescue/recovery workers (SMR = 0.33; 95% CI: 0.12, 0.72; *n* = 6), and in community members (SMR = 0.60; 95% CI: 0.42, 0.82; *n* = 38).

In addition to the previously described limitations inherent to composite outcomes, mortality studies, and external comparisons, this paper did not control for important risk factors for CVD mortality, including body mass index (BMI), alcohol use, family history of heart disease, and PTSD status. Therefore, residual confounding cannot be ruled out.

b. Stein et al. [2016]

Stein et al. [2016] examined mortality patterns in a longitudinal study of rescue and recovery workers (*n* = 30,947) in the GRC followed between 2002 and 2011 (164,563 person-years). The underlying cause of death was identified via linkage to the NDI. Deaths were grouped according to the NIOSH LTAS [Robinson et al. 2006; Schubauer-Berigan et al. 2011], with Major 17 (other diseases of the circulatory system) indicating the outcome of interest. The SMRs were calculated,

controlling for age, sex, race, and calendar period. A proportionate mortality ratio (PMR) was also calculated with similar standardization.

The cohort was mostly male (85.2%), non-Hispanic white (63.3%), with an average age on September 11, 2001, of 39 years. The SMR for Major 17 was significantly below expectation (SMR = 0.19; 95% CI: 0.08, 0.37; *n* = 8 deaths). The PMR also provided no evidence of increased risk for Major 17 (PMR = 0.44; 95% CI: 0.19, 0.87).

Stein et al. [2016] had the previously described limitations inherent to composite outcomes, mortality studies, and external comparisons. An additional limitation is the use of a PMR as a risk measure, which relies heavily on strong assumptions that may not be valid for this population [Miettinen and Wang 1981]. Furthermore, since the PMR is the proportion of cases classifiable to a particular cause in relation to the overall number of disease cases, it is affected by all other causes of death, which could lead to biased estimates of risk. Without additional information, the magnitude and direction of bias is not clear.

c. Wilkenfeld et al. [2016]

Wilkenfeld et al. [2016] conducted a cross-sectional survey that assessed self-reported medical co-morbidities, including stroke and neuropathic symptoms, among a convenience sample of subjects (*n* = 255), comparing those with 9/11 exposures (*n* = 139) to those without 9/11 exposures (*n* = 116). The survey was distributed online to responders, survivors, and their families and to some faculty and staff at Queens College. Hard copies of the questionnaire were also distributed to WTC responders treated at New York University (NYU) Langone Hospital Long Island's Occupational/Environmental Medicine Division and among people visiting NYU Langone Hospital Long Island-associated health facilities.

9/11 exposure was measured as a binary variable (exposure vs. no exposure). The difference in frequencies of selected medical comorbidities (including stroke) between persons with 9/11 exposure and persons without 9/11 exposure was assessed via Fisher's exact test.[40]

The frequency of stroke among persons with WTC exposure was 0.043 (*n* = 6) and 0.026 among those with no WTC exposure (*n* = 3). The difference was not statistically significant (*p* = 0.52). These findings should be interpreted with caution. Fisher's exact test evaluates whether an association exists, while risk estimates such as the odds ratio (OR), which were not calculated in this study, measure the strength of that association. Furthermore, only a small number of stroke cases were reported for each comparison group. Information on date of stroke onset was not provided, so it was not

40 Fisher's exact test is a statistical significance test used to determine whether there is a nonrandom association between two categorical variables in a contingency table, typically a 2×2 table. It is called "exact" because it calculates the exact probability of observing the data. Fisher's exact test only produces a *p*-value, i.e., it tells whether the association between two categorical variables is statistically significant (unlikely to arise by chance given fixed margins). It says nothing about the strength of the association. *See* Agresti [2002].

clear if stroke had a pre-9/11 onset. Because the study is based on a cross-sectional survey, it cannot establish temporality or support causal inferences. Exposure was measured as a binary variable (yes/no), with no information provided regarding the nature, intensity, or duration of exposure among respondents who reported being exposed to the dust cloud. Additionally, the survey assessed only self-reported presence of the comorbidity (e.g., stroke), and no medical verification was obtained. Finally, the survey sampling frame[41] was not described, making it difficult to assess the representativeness of the study population and limiting the generalizability of the findings. Wilkenfeld et al. [2016] included both responders and survivors, but the authors did not report how many of each participated. Based on the numerous limitations of the study, Wilkenfeld et al. [2016] was removed from further consideration.

d. Jordan et al. [2018]

Jordan et al. [2018] expanded and extended follow-up of a previous longitudinal mortality study, Jordan et al. [2011a], adding 5 years through 2014. The study population comprised WTCHR enrollees (*n* = 69,923) categorized as rescue/recovery workers (*n* = 29,280) and lower Manhattan area community members (*n* = 39,643). Information on the underlying cause of death was obtained by linkage with NDI. Deaths were classified according to NIOSH LTAS Major 17 (other diseases of the circulatory system) [Robinson et al. 2006; Schubauer-Berigan et al. 2011].

Among rescue/recovery workers there were 44 deaths from Major 17 and mortality was significantly decreased (SMR = 0.66; 95% CI: 0.48, 0.89). Among community members there were 101 deaths from Major 17 and mortality was non-significantly decreased (SMR = 0.84; 95% CI: 0.69, 1.02). Jordan et al. [2018] had the previously described limitations inherent to composite outcomes, mortality studies, and external comparisons, as well as those limitations described for Jordan et al. [2011a].

e. Li et al. [2023]

Li et al. [2023] conducted a longitudinal mortality study of 60,631 WTC rescue and recovery workers from FDNY, GRC, and WTCHR. The pooled cohort included adults with complete race/ethnicity data and excluded individuals who enrolled late, were very old, or died early in follow-up to reduce selection bias. To avoid duplication of study participants, pooling followed a hierarchy that included FDNY members first, followed by GRC members, then WTCHR enrollees. Follow-up extended through 2016 (697,943 person-years). Vital status and causes of death were obtained via NDI, and "other diseases of the circulatory system" was defined according to NIOSH LTAS Major 17

41 The term "sampling frame" refers to the members of a population who are eligible to be included in a given sample, i.e., drawing a "frame" around those cases that are acceptable for inclusion in the population sample. The term is commonly used in survey sampling, where it is associated with a countable listing of all the data sources in the population that are accessible for sampling. *See* Mooney and Garber [2019].

[Robinson et al. 2006; Schubauer-Berigan et al. 2011].

The cohort was predominantly male, non-Hispanic White, and never-smokers. There were 93 deaths involving Major 17, and mortality was substantially lower than expected based on U.S. (SMR = 0.34; 95% CI: 0.28, 0.42) or state (SMR = 0.44; 95% CI: 0.36, 0.55) referent rates, indicating a strong healthy worker effect.

Strengths included large sample size, long follow-up, and appropriate analytic methods. Limitations include those previously described and inherent to composite outcomes, mortality studies, and external comparisons.

f. Singh et al. [2023]

Singh et al. [2023] conducted a longitudinal mortality study of 10,786 WTC exposed FDNY male firefighters and 8,813 male firefighters from Philadelphia, San Francisco, and Chicago who were not exposed to the WTC disaster. All participants were employed on September 11, 2001, and follow-up was extended through 2016, totaling 163,583 person-years. Mortality information was obtained from NDI, and causes of death were categorized using the NIOSH LTAS system, with Major 17 (other diseases of the circulatory system) serving as one of the outcomes of interest. SMRs were calculated separately for the exposure groups using U.S. national mortality rates as the referent, and rate ratios comparing FDNY to non-WTC exposed firefighters were estimated with Poisson regression adjusting for age on September 11, 2001, and race/ethnicity. The study also considered an internal exposure response analysis among FDNY firefighters, but this was limited to all-cause mortality and did not include stroke or "other diseases of the circulatory system"-specific modeling.

At enrollment, the FDNY cohort was mostly non-Hispanic White (93.8%) and never smokers (66.4%). The average age on September 11, 2001, was 40.4 years. For FDNY firefighters, the SMR for Major 17 was 0.18 (95% CI: 0.08, 0.35; n = 8) compared with 0.38 (95% CI: 0.24, 0.56; n = 23) among the non-WTC-exposed firefighters with both groups compared with the general population. There was lower mortality from Major 17 among FDNY firefighters compared with non-WTC-exposed firefighters (adjusted relative rates [RR] = 0.74; 95% CI: 0.66, 0.84).

Overall, Singh et al. [2023] provided no evidence of increased risk of other diseases of the circulatory system among FDNY firefighters compared with the general population nor with an external group of Philadelphia, San Francisco, and Chicago career firefighters. Methods used were appropriate for the available data. A unique strength of the study is its use of a similarly employed control group in RR analyses. Important limitations included those previously described and inherent to composite outcomes, mortality studies, and external comparisons.

g. Parvin et al. [2026]

Parvin et al. [2026] conducted a longitudinal study that compared

mortality risk between 9/11 responders enrolled in the WTC Health Program versus non-enrolled responders. The study did not assess the association between 9/11 exposure and mortality. The study used a subset (*n* = 28,430) from the established combined cohort of 9/11 responders (*n* = 69,100) that includes responders from FDNY, the GRC, and the WTCHR. The subset consists of only those responders who were submitted by the WTCHR to the combined cohort, since all members of this subset had WTCHR-collected comorbidity data. This helped to ensure uniformity of the captured comorbidity data. These WTCHR members were stratified into two groups: FDNY/GRC members who had enrolled in the WTC Health Program by December 31, 2016 (i.e., WTCHR members who were also WTC Health Program members, *n* = 9,467) vs. non-FDNY/non-GRC members (i.e., WTCHR members who never enrolled in the Program or enrolled after December 31, 2016, *n* = 18,963). The studied sample excluded those who were < 18 years on September 11, 2001, those who died or turned 85 years or older within the first year of enrollment, those who had unknown smoking status, unknown race/ethnicity, or were incapacitated and required a proxy to respond to the WTCHR questionnaires. Among the 9,467 FDNY/GRC members, 4,315 (46%) initially enrolled in the WTCHR before joining FDNY or GRC.

Vital status was ascertained through December 31, 2020. Data were collected on several comorbidities in the WTCHR's Waves 1 through 4, which were conducted between 2003 and 2016. The comorbidities included aerodigestive disorders, mental health conditions, cancer, and CVD, including stroke, based on self-reported diagnosis by a healthcare professional. Smoking status and baseline demographics (e.g., sex, race/ethnicity, and 9/11 exposure) were obtained from the cohort in which the participant first enrolled (FDNY, GRC, or WTCHR). Cox proportional hazards regression was used to estimate HRs for the association between WTC Health Program membership status and all-cause mortality. They also examined smoking-related mortality, a composite outcome variable that included the following types of underlying cause of death: (a) smoking-related cancers; (b) CVD (including CeVD and other vascular diseases); (c) metabolic diseases (diabetes mellitus); and (d) smoking-related non-malignant respiratory diseases. For analysis of smoking-related mortality, they used cause-specific hazard regression models to account for competing risks.

Compared to non-members, WTC Health Program members were more likely to be male, in the age groups of 30 to 39 years and 40 to 49 years on September 11, 2001 (they were less likely to be 18 to 29 years of age on September 11, 2001), non-Hispanic White, never smokers, and to have arrived earlier at the WTC site and performed tasks on the pile. In addition, WTC Health Program members had a statistically significantly higher proportion of post-9/11 comorbidities compared to non-WTC Health Program members. However, non-members had significantly higher pre-September 11, 2001, diagnoses of certain conditions, including asthma, depression, and cardiovascular

conditions. Male WTC Health Program members had a significantly lower risk of all-cause mortality compared to male non-members after adjusting for demographics, smoking status, and 9/11 exposure (Model 2: adjusted hazard ratio (aHR) = 0.85; 95% CI: 0.75, 0.96), but not among women (Model 2: aHR = 1.16; 95% CI: 0.80, 1.68). WTC Health Program members had a lower risk of smoking-related mortality compared to non-members, after adjusting for demographics, smoking status, 9/11 exposure and comorbidities (aHR = 0.83; 95% CI: 0.69, 0.99). Risk was not modified by gender.

When determining all-cause and smoking-related mortality risk, it appears the authors did not adjust their HRs by using more recent smoking status. Instead, they obtained smoking status at first enrollment only, which was reported to be 16% among WTC Health Program members and 18% among non-WTC Health Program members. Smoking rates dropped dramatically among WTC Health Program members and on December 31, 2024, were 4.5% at FDNY and 6.3% at GRC (internal data). It is not known if non-WTC Health Program members were similarly encouraged/supported to quit smoking. The sharp smoking reductions among WTC Health Program members may explain the lower risk of smoking-related mortality among WTC Health Program members. The authors also speculated that better healthcare access among WTC Health Program members may have contributed to all-cause and smoking-related mortality risks. Because this study did not assess the association between 9/11 exposure and mortality, it was removed from further consideration. Instead, Parvin et al. [2026] compared mortality risk between WTC Health Program members versus non-members who were enrolled in the WTCHR.

C. Studies Considered High-Quality

The Science Team determined that nine of the 18 identified studies were considered high-quality for this evaluation. Six are newly identified high-quality studies published between March 2019 and May 2026 [Cohen et al. 2019; Colbeth et al. 2020; Sloan et al. 2021; Yu et al. 2021; Alper et al. 2021; Mueller et al. 2024]. Three other studies [Jordan et al. 2013; Yu et al. 2018; Remch et al. 2018] were previously reviewed in the February 2019 evaluation of **Petition 020** and under the current version of the *Policy and Procedures* have sufficient validity indicators to be considered high-quality studies [NIOSH 2026a].[42]

1. Previously Reviewed High-Quality Studies

Jordan et al. [2013], Remch et al. [2018], and Yu et al. [2018] were previously reviewed, with findings and notable limitations discussed in detail in the Administrator's published decision on **Petition 020**.[43] *See* **Table 2**. These three high-quality studies were considered informative for this evaluation and are summarized below.

42 A previous version of the *Policy and Procedures* was in effect at the time the evaluation of **Petition 020** was published [NIOSH 2017]. The 2017 version of the *Policy and Procedures* did not make mention of high-quality studies. However, under the current *Policy and Procedures* [NIOSH 2026a], these three studies are considered high-quality and, as a result, merit further evaluation.

43 *See* supra, note 2

a. Jordan et al. [2013]

Although not contributing to the previous synthesis for **Petition 020** for reasons described in the related docket, Jordan et al. [2013] is a high-quality longitudinal study of CVD hospitalizations, including CeVD, in a cohort of 46,346 adult WTCHR enrollees residing in New York State that provided some information on the risks of stroke. The study examined the association between CeVD (ICD 9 codes 430–438) and multiple predictors, such as PTSD, injuries, and WTC-dust exposure in a large cohort of WTCHR enrollees with complete exposure information (*n* = 46,346) followed through 2010. The CeVD composite outcome included stroke, but also CVD such as subdural hemorrhage, hypertensive encephalopathy, and cerebral arteritis. Ascertainment was made by linking participants to the New York State hospital discharge reporting system that is managed by the Statewide Planning and Research Cooperative System (SPARCS). Probable PTSD status (yes/no) was determined at enrollment using the 17-item PTSD checklist that inquired about 9/11-specific psychological symptoms (PCL-S). Injury was defined as self-report of being injured on September 11, 2001 (yes/no). Dust cloud exposure was defined as being in the dust cloud on September 11, 2001 (yes/no). Ordinal categories (high, intermediate, low) of 9/11-related exposure were derived from rescue/recovery worker responses to questions on arrival time, location, type, and duration of work. Analyses were conducted using proportional hazards regression, adjusting for age, race/ethnicity, smoking, education, marital status, and self-reported, physician-diagnosed hypertension and diabetes. Analyses were stratified by sex and by enrollee type. Primary predictors (i.e., PTSD, injury on September 11, 2001, and WTC-dust exposure) were examined separately.

The cohort comprised slightly more males (59.7%) than females and more non-Hispanic White persons (59.7%) compared to other races. Nearly half were college educated (48.1%). There were 284 CeVD hospitalizations during 302,742 person-years of observation. The study reported a statistically significant association between PTSD status and CeVD in men but not women. There was little evidence of an association between CeVD and dust exposure or injury. *See* **Table 4**.

Study strengths include the longitudinal design, objective measures of CeVD incidence, and CeVD risk estimates available by sex and enrollee type. Notable limitations include small numbers of events in some analyses (e.g., analyses of female responders), limited information on some potential risk factors (e.g., family history of CeVD and dyslipidemia), lack of controlling for PTSD in analyses of other predictors, lack of objective exposure measures (exposure data obtained from WTCHR enrollees were self-reported), and potential under ascertainment from persons hospitalized in institutions that are not included in SPARCS (i.e., federal or psychiatric hospitals, and hospitalizations that occurred outside of New York State). The

directionality of potential bias from under ascertainment has not been investigated, i.e., it is not known whether ascertainment is differential with respect to exposure status. Finally, the grouping of stroke with other CeVD precluded differentiation of stroke from other CeVD. The use of CeVD as an outcome was noted as an important limitation in the previous evaluation for **Petition 020**. Lastly, models examining the effects of 9/11 dust and injuries did not consider the effects from PTSD. Probable PTSD was associated with CeVD in this study, suggesting its importance as a contributing factor; however, PTSD was not accounted for in models examining the relationship between 9/11 exposure and CeVD outcomes. Based on this limitation, the authors acknowledged that the study could not determine whether "… PTSD was part of the causal pathway between 9/11-related environmental exposures and CVD hospitalizations or whether PTSD and rescue/recovery-related exposures were independent risk factors."

b. Remch et al. [2018]

Remch et al. [2018] conducted a prospective longitudinal study examining 5,971 (83% male) responders who were recruited from two WTC Health Program Clinical Centers of Excellence between January 2012 and June 2013 and followed at least once per year through 2016 to determine whether probable PTSD and exposure to 9/11 agents are risk factors for a composite outcome of MI and stroke. Outcomes included "recurrent" events, which were defined as an event occurring in persons with a previous event prior to observation but after 2001. Findings restricted to stroke were limited to examining its association with recognized cardiovascular risk factors and PTSD. The main analyses used outcomes obtained from self-report; however, medical chart review was conducted for about 60% of the study group. Additional analyses restricted to New York State residents (n = 5,454) were conducted using outcome information from linkage to SPARCS. Multiple indices of 9/11 exposure were derived from information in self-administered questionnaires. Analyses were conducted using proportional hazards regression adjusting for sex, age, hypertension, total cholesterol, BMI, tobacco use, and respirator use. Models examining the association between 9/11 exposure and MI/stroke also adjusted for probable PTSD as an independent risk factor. PTSD was assessed using the PTSD checklist for civilians (PCL-C) [Ruggiero et al. 2003] that included a preamble for relating answers to participation in the WTC cleanup. PTSD was defined either dichotomously (PCL-C score ≥ 44) or by treating PCL-C scores as a continuous variable.

Participants were mostly male (82.7%), non-Hispanic White (54.1%), and college-educated (74.6%). The prevalence of probable PTSD was 19.9% in men and 25.9% in women. There were 53 stroke cases during the observation period and 15 of these were recurrent. There were 70 reported cases of MI (20 recurrent). When restricted to persons linked to SPARCS, all incident MI and stroke cases identified in interviews were also present in the hospital discharge system; however, 49

hospital discharge events were not found in active follow-up (i.e., not self-reported). The distribution of missing discharge events by WTC dust exposure was not reported.

Findings restricted to stroke were not available for analyses of WTC dust exposure indices; therefore, results are reported for MI and stroke combined. Overall, there was little evidence supporting an association between MI/stroke and indices of exposure to WTC dust. In contrast, the authors reported evidence of PTSD as a strong risk factor for both self-reported stroke (HR = 2.51; 95% CI: 1.39, 4.57) and MI (HR = 2.22; 95% CI: 1.30, 3.82). The association between PCL-C score and MI/stroke persisted in analyses treating PCL-C score as a continuous variable. Interestingly, associations between stroke and many known risk factors were not observed, including blood pressure, BMI, total cholesterol, and smoking.

Remch et al. [2018] has multiple strengths, including the prospective cohort design, partial validation of outcomes by medical chart review, and additional validation via linkage to hospital discharge records. There are also important limitations. First, the observation period was limited to 4 years beginning more than a decade after September 11, 2001; therefore, stroke risks between 2001–2012 are not clear and power to estimate risks afterwards is limited. Second, few results excluding persons with recurrent cases were reported. The effect on risk estimates from including persons with stroke events prior to observation is unclear. Third, the ascertainment of recurrent cases is not clear; therefore, completeness of information on stroke prior to observation is uncertain. Fourth, findings from analyses using a composite outcome of MI and stroke are difficult to interpret with respect to stroke given that MI contributed to 58% of the events. Finally, a strength of the study was control for PTSD as an independent risk factor; however, residual effects from incomplete control resulting from model misspecification cannot be ruled out [Schisterman et al. 2009].

c. Yu et al. [2018]

Yu et al. [2018] is a longitudinal analysis of 42,527 adult WTCHR enrollees completing Wave 1 and 2 surveys. Self-reports of WTC dust exposure and stroke diagnosis subsequent to September 11, 2001, were obtained from the four WTCHR survey Waves conducted between 2003 and 2016. Intense exposure was defined as having been in the WTC dust cloud and reporting at least one of the following: inability to see more than a few feet; difficulty walking; difficulty finding shelter; being covered with dust; or loss of hearing. Minimal or no-exposure was defined as being in the WTC dust but without experiencing intense exposure, or no WTC dust exposure at all. After adjusting for sociodemographic characteristics, and risk factors for stroke (smoking and history of hypertension and/or diabetes), the study found that self-reported stroke was higher among enrollees with intense dust cloud exposure when compared with those with minimal

or no dust exposure (aHR = 1.30; 95% CI: 1.10, 1.53). After adjusting for PTSD status, the risk of self-reported stroke among enrollees reporting intense dust cloud exposure was still modestly increased (aHR = 1.20; 95% CI: 1.02, 1.42) compared to those with minimal or no dust cloud exposure.

The study has numerous strengths, including the longitudinal design, a large number of participants, a detailed assessment of dust cloud exposure, and evidence of external validity as provided by the observed associations between stroke and traditional stroke risk factors (i.e., age, smoking, diabetes, and hypertension). A limitation is that the authors did not control for several important risk factors that might mediate the association between 9/11 exposures and stroke, including history of dyslipidemia, alcohol consumption, and family history of heart disease. In addition, the outcome was self-reported and not objectively confirmed.

Collectively, these four studies reported some evidence suggesting a possible association between 9/11 dust exposure and stroke. However, findings were inconsistent. One study reported significantly positive associations between 9/11 exposure and self-reported stroke in WTCHR enrollees [Yu et al. 2018], while the other two studies with medical confirmation of composite outcome variables failed to find an association between those composite outcome variables and any 9/11 exposure measure [Jordan et al. 2013; Remch et al. 2018].

2. Newly Identified High-Quality Studies

Six studies identified in the review of the literature were determined to be high-quality studies in accordance with the *Policy and Procedures* and were published after the **Petition 020** evaluation was completed in February 2019 [Cohen et al. 2019; Yu et al. 2021; Colbeth et al. 2020; Alper et al. 2021; Sloan et al. 2021; Mueller at al. 2024].[44],[45] *See* **Table 3**.

a. Cohen et al. [2019]

Cohen et al. [2019] conducted a longitudinal cohort study of FDNY male firefighters (*n* = 9,796) to assess whether exposure to 9/11 agents was associated with elevated CVD risk. The study population included male firefighters who were on active duty on September 11, 2001, and arrived at the WTC site within the first two weeks. The study examined total CVD incidence that was ascertained by finding any of the following physician-documented diagnoses in the FDNY electronic medical record: MI, stroke, unstable angina, coronary artery surgery or angioplasty, or CVD death. As such, the outcome was a composite of various types of CVD, which included stroke. Two separate instruments were used to determine PTSD status over the course of study. Status was determined from the earliest of either the PTSD checklist as modified by FDNY (PCL-m) administered during 2001–2005 [Berninger et al. 2010], or the 17-item 9/11-specific PTSD checklist

44 Colbeth et al. published a correction to their 2020 article in 2023. *See*: Colbeth et al. [2023].
45 *See Policy and Procedures*, Section III.C. [NIOSH 2026a].

(PCL-S) [Ruggiero et al. 2003] administered thereafter.[46] For the latter (comprising only 6% of participants), a score ≥ 44 was considered probable PTSD as in other studies. In contrast to the PCL-S, the PCL-m included 14 binary choice questions modified for 9/11 context. Probable PTSD for PCL-m was determined by indication of symptoms within each of three PTSD symptom groups identified in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* [APA 1994]. The authors reported that the PCL-S and the PCL-m provided similar results, although results were not shown. Statistical analyses were conducted using proportional hazards regression models adjusted for age, race/ethnicity, and baseline values of BMI, hypertension, hypercholesterolemia, diabetes mellitus, smoking, and probable PTSD.

The study population was mostly non-Hispanic White (94.2%), with a mean age of 40.3 years. Probable PTSD prevalence was 10.4%. There were 489 CVD events during the observation period (147,680 person-years), of which nearly all (87.3%) were attributable to IHD, followed by stroke (12.5%). The authors reported modest, but statistically significant estimates of an association between CVD and different measures of 9/11 exposure in FDNY. For example, there was a 44% increase in CVD risk in firefighters reporting to the scene on the morning of September 11, 2001, compared to firefighters reporting between September 12 and 24, 2001 (HR = 1.44; 95% CI: 1.09, 1.90).

Cohen et al. [2019] has several important strengths. First, the FDNY's firefighter cohort is large and longstanding, having been established prior to September 11, 2001, and followed through 2017. This cohort included only firefighters who were active duty and arrived at the WTC within two weeks of September 11, 2001; therefore, they may be more likely to be healthy and free of clinical CVD at that time. Second, FDNY firefighters, on average, are likely to have higher 9/11 exposure levels compared to other 9/11-exposed population subgroups; therefore, the cohort offers greater statistical power to observe an exposure-response association. Third, CVD outcomes were confirmed using FDNY medical records rather than relying on patient self-report. Fourth, although a composite CVD outcome was defined, the primary outcome comprised mainly IHD, thereby reducing uncertainty in the outcome definition. Fifth, models attempted to control for the effects of probable PTSD. Lastly, information was available on a large set of known CVD risk factors, which were used to derive covariates for multivariable analysis. Results from these analyses appeared consistent with current knowledge of these risk factors.

Cohen et al. [2019] also has several limitations. The key limitation of this study is the inability to conduct cause-specific analyses of stroke, although stroke events were included within the composite CVD outcome. Second, only male firefighters were examined;

46 Email correspondence conducted on September 4, 2025, with Rachel Zeig-Owens, the corresponding author of Cohen et al. [2019], indicated that from 2005 through 2007, the specific traumatic event used in PCL-S was the September 11, 2001, terrorist attack. However, starting in 2008, the FDNY member could select their own worst traumatic event and that event was populated into the PCL-S questions. Singh et al. [2020] observed that despite having this choice, 78% selected September 11, 2001, as their most traumatic event.

therefore, generalization is limited. Third, objective measures of exposure were not available; therefore, exposure misclassification from recall errors cannot be ruled out. Efforts to examine potential bias from exposure misclassification are lacking. Fourth, the study lacked exact dates of some CVD events, which the authors suggest may have biased risk estimates toward the null. Fifth, occupational exposure from firefighting that occurred after September 11, 2001, was not considered and investigations into whether these exposures are differentially distributed across exposure groups have not been conducted. Therefore, confounding by other occupational (or environmental) exposure cannot be ruled out. Sixth, the relationship between PTSD, WTC dust exposure, and stroke is not clear; therefore, model misspecification cannot be ruled out. There was no evidence of an association between PTSD and CVD; therefore, the potential for bias from PTSD was suggested to be small. However, the Science Team noted that dissimilar methods were used to ascertain probable PTSD status over the course of the study, with most participants assessed using the earlier PCL-m method. Although efforts to examine the potential effects on risk estimates from mixing PTSD screening methods were briefly described, the effect (if any) was not sufficiently elucidated by the study authors. Finally, estimates did not control for important risk factors, such as alcohol consumption and family history of heart disease, which might confound an association between 9/11 exposures and CVD.

b. Colbeth et al. [2020]

The study by Colbeth et al. [2020] is a longitudinal design examining all-cause and cause-specific mortality patterns in a cohort of FDNY responders (*n* = 15,431) followed through 2017. The study obtained the underlying cause of death by matching to NDI and grouped deaths by the NIOSH LTAS 119-cause map [Robinson et al. 2006; Schubauer-Berigan et al. 2011]. CeVD was defined by NIOSH Minor Category 60, which included TIAs and related syndromes (ICD 10 codes G45.0–G45.2, G45.4–G45.9) and all cerebrovascular disease (I60–I69). SMRs and associated 95% confidence intervals were calculated, controlling for age, sex, race/ethnicity, and calendar period. The U.S. population was the referent group used in external comparisons. There were no reported internal analyses examining the exposure-response association among cohort members for CeVD mortality.

Participants were largely male (96.8%), firefighters (86.0%), non-Hispanic White (87.2%), and never-smokers (60.9%). There were 10 CeVD deaths observed over the follow-up period (2001–2017). The mortality rate among FDNY responders was significantly decreased when compared with the U.S. population (SMR = 0.20; 95% CI: 0.09, 0.36). The deficit in risk was likely due to selection bias from large differences between cohort members and the referent group, such as smoking rates, employment, and access to healthcare.

Colbeth et al. [2020] has several strengths. The study cohort is

relatively large and was followed over a long period. The study methods used are well-established and appropriate for the available data. However, there are notable limitations. First, internal analyses restricted to stroke were not conducted. Second, there were only 10 CeVD deaths observed over the follow-up period (2001–2017). Third, the cohort comprised mostly White males; therefore, generalizability to other 9/11 populations is limited. Fourth, the authors did not control for several important risk factors that might mediate the association between 9/11 exposures and CeVD, such as PTSD, dyslipidemia, hypertension, alcohol consumption, and family history of heart disease. Finally, markedly improved survival among CeVD patients due to medical advancements and increased access to medical care means fewer deaths available for study and a potential underestimation of CeVD risk when using mortality as the endpoint. For example, as noted above, there continues to be lower than expected CeVD mortality among FDNY members, which is likely because of improved health due to physical requirements for employment (i.e., a healthy worker effect), improved lifestyle, and access to physical and mental health annual monitoring examinations, screening tests, diagnostic procedures and treatments, and disease management counseling as part of the WTC Health Program.

c. Alper et al. [2021]

Alper et al. [2021] conducted a longitudinal study that investigated the agreement between survey and hospitalization data with respect to estimates of disease prevalence and exposure-chronic disease associations. The investigation of exposure-chronic disease associations included an assessment of four measures of 9/11 exposure and select health outcomes, including stroke. To be eligible for inclusion in this study of WTCHR enrollees, the enrollee had to have completed all of the first four WTCHR survey Waves[47] and had to have resided in New York State at Waves 2 and 3. The resulting study group included 18,206 persons (the authors did not report how many were area workers, rescue/recovery workers, residents, or passersby).

The four measures of 9/11 exposure self-reported at Wave 1 included: (1) probable PTSD defined as a 17-item PCL-S score ≥ 44 (yes/no) [note that the Program does not consider PTSD to be a 9/11 agent; instead, PTSD is a covered condition]; (2) caught in the dust cloud on 9/11 (yes/no); (3) having experienced one or more injuries on September 11, 2001 (yes/no); and (4) witnessed three or more traumatic events on September 11, 2001 (e.g., seeing planes hit buildings, witnessing people jumping from buildings) (yes/no). Two binary CVD outcomes were created: (1) self-reported stroke that was diagnosed by a health professional between 2002 and 2015 and was reported by the enrollee in any of Waves 1 through 4; and (2) stroke identified by linking participants to SPARCS data for the period 2002–2015 and finding a

47 The initial WTCHR survey was conducted in 2003–2004 (Wave 1), and subsequently in 2006–2007 (Wave 2), 2011–2012 (Wave 3), and 2015–2016 (Wave 4).

hospitalization or emergency department visit that was assigned any of the following ICD-9 codes for CeVD: 430.XX, 431.XX, 432.XX, 435.XX, 436.XX, 433.01, 433.10, 433.11, 433.21, 433.31, 433.91, 434.00, 434.01, 434.11, 434.91.[48] Analyses of the exposure-stroke association were conducted using logistic regression adjusting for sex, age on 9/11, race/ethnicity, and education. The authors also investigated the difference between the ORs based on the self-report versus SPARCS outcomes on the log scale (i.e., the difference between the β)[49] for all four exposure-disease pairs and assessed the statistical significance of those differences.

Participants included more males (60.5%) than females, were aged 25 to 44 years on September 11, 2001, (51%), non-Hispanic White (70%), and college-educated (52%). About 15% of participants had probable PTSD. The prevalence of stroke between 2002 and 2015 was 2.4% based on self-report and 1.1% based on SPARCS (the counts of these outcomes were not reported) (*kappa* = 0.35, which is considered to represent a fair amount of agreement). For the self-reported stroke outcome, the ORs for three exposure measures were significantly elevated: PTSD (OR = 1.9; 95% CI: 1.5, 2.4), dust cloud exposure (OR = 1.5; 95% CI: 1.2, 1.8), and witnessing traumatic events on September 11, 2001 (OR = 1.4; 95% CI: 1.1, 1.7). For the SPARCS stroke outcome, the only exposure measure with a significantly elevated OR was PTSD (OR = 1.5; 95% CI: 1.1, 2.2). *See* **Table 5**. For all four 9/11 exposure variables, the risk estimates for the two stroke outcomes (self-report versus SPARCS) were not significantly different, suggesting the absence of measurement bias.

A notable strength of Alper et al. [2021] was that it used a large prospective cohort and used objective outcome data (i.e., SPARCS). Another strength was the comparison of self-reported and hospitalization data sources for the stroke outcome. Stroke prevalence was 54% higher using self-reported data.

The study by Alper et al. [2021] also had notable limitations. First, the study used a restricted sample of the WTCHR population who completed Waves 1, 2, 3, and 4. The study population comprised only 25.5% of all enrollees; therefore, representativeness is a concern, as well as bias through attrition across the Waves. Second, there was a lack of detailed information on injuries that occurred on September 11, 2001 (e.g., no information on injury severity, number of injuries, body location, and whether the injury required treatment). There was also a lack of objective measures for the other exposures; therefore, the potential for biases from errors in ascertainment and exposure assignments cannot be ruled out. Third, several risk factors were not controlled for, including BMI, smoking, hyperlipemia, diabetes

48 Alper et al. [2021]. Additional file 1: Appendix 1 (ICD-9 Codes for Chronic Diseases). *See* Supplementary Information at https://link.springer.com/article/10.1186/s12874-021-01358-y#Sec15. The "XX" in some ICD-9 codes represents two placeholder digits used to specify additional details about the diagnosis. This notation is commonly used in research documents to refer to the entire range of codes under a category rather than a specific one. The "XX" denotes all subcodes within those stroke categories without enumerating each one.

49 The beta coefficient (β) represents the change in the log odds of the outcome for a one-unit increase in the value of the exposure. *See* Szumilas [2015].

and hypertension; therefore, the potential for residual confounding cannot be ruled out. Fourth, a single source of hospitalization data (i.e., SPARCS) was used which does not capture out-of-state hospitalizations, which could lead to reduced hospitalized stroke prevalence estimates.

d. Sloan et al. [2021]

Sloan et al. [2021] conducted a large longitudinal study of 37,723 WTC rescue and recovery workers enrolled in the GRC, following participants from 2002–2019. CVD outcomes were based on self-reported physician diagnoses or treatment for CAD, MI, stroke, or congestive heart failure. WTC exposure was categorized by arrival date and dust cloud exposure.

Participants were mostly male (86.3%), non-Hispanic White (54.7%), and never-smokers (57.7%). IHD was most prevalent, with CAD and MI comprising 67% of CVD events. A total of 2,385 GRC members reported being treated for CVD, of which 670 (28%) were treated for stroke. Using proportional hazards models stratified by sex and adjusted for major CVD risk factors, the study found significantly increased CVD risk in workers with very high or high exposure compared with those with low/intermediate exposure. In a combined, fully adjusted model, the HR was 1.12 (95% CI: 1.03, 1.22). However, adjustment for employment in "protective services" (e.g., police, military) — a group comprising over half the cohort — substantially reduced the exposure–response association. Protective services work itself was a strong predictor of CVD for both men (HR = 2.16) and women (HR = 2.94), suggesting notable confounding by occupation. *See* **Table 6**.

Study strengths of Sloan et al. [2021] include large cohort size, inclusion of many female responders, and observation up to 17 years post-September 11, 2001. The methods were appropriate for the available data. This is the first study adjusting for confounding by occupation in protective services on September 11, 2001, which showed a marked effect on risk estimates.

However, this study also has several limitations. First, the study did not conduct analyses restricted to stroke outcomes; therefore, interpretation of stroke risk is uncertain. Second, objective measures of exposure and outcome were not available; therefore, bias in risk estimates from errors in recall cannot be ruled out. Third, study participants were only followed until their most recent monitoring exam, and over time there was a decreasing number of members who returned to the clinic for their annual reexamination. As such, cases of CVD are likely under-reported. Fourth, employment in protective services confounded the association between 9/11 exposure and CVD, although evidence of increased risk remained after adjustment. Nevertheless, residual confounding cannot be ruled out. Furthermore, the true relationship between multiple

explanatory variables and the dependent variable may not be accurately depicted by a simple covariate model. For example, the authors cautioned against overinterpretation given observed violations of the proportional hazards assumption (i.e., the effect measure for any predictor is constant over time) for some covariates, including smoking, cholesterol, and BMI status. Violation of proportional hazards assumption may indicate that the model specification used poorly describes the true association. The authors also acknowledged comorbidities and potential risk factors may lie on the causal pathway (a causal pathway refers to the sequence of events and mechanisms through which a cause leads to an effect, particularly in understanding how certain exposures influence health outcomes) between 9/11 exposures and CVD; therefore, standard covariate adjustment might have distorted risk estimates. Fifth, the authors did not control for important risk factors that might bias estimates of the association between 9/11 exposures and CVD, including PTSD status, alcohol consumption, and family history of heart disease. Lastly, as recognized by Sloan et al. [2021], entry into the GRC is voluntary and membership is more diverse compared with the FDNY cohort. The GRC has observed diminishing numbers of members attending monitoring visits over time. These factors suggest a potential for bias from self-selection. The extent to which findings in this cohort are representative of the population of all 9/11-exposed general responders is unclear.

e. Yu et al. [2021]

As a follow-up to the previous study of self-reported stroke in the WTCHR [Yu et al. 2018], Yu et al. [2021] examined stroke hospitalizations, PTSD, and 9/11-related dust exposure in a cohort of 29,012 WTCHR enrollees followed between 2003–2016. The aim of this study included validation of the previous study findings by supplanting self-reported information with hospitalization data that improved case ascertainment, as well as allowed for differentiation by stroke subtype. WTCHR enrollees aged ≥ 18 years and who were residents of New York State on 9/11 and completed the Wave 1 (2003–2004) and Wave 2 (2006–2007) surveys were linked to hospital inpatient data in SPARCS between 2000 and 2016. If available, data from Waves 3 (2011–2012) and 4 (2015–2016) were also used. Participants with stroke prior to WTCHR enrollment (their interview date in Wave 1) were excluded. Stroke was defined as having one or more inpatient records with a stroke diagnosis code in the hospitalization database. Strokes were classified as ischemic (including TIA) or hemorrhagic. Time at risk was from enrollment through the earliest of the first stroke or study end (2016). As in the previous study [Yu et al. 2018], PTSD status was assessed as a score ≥ 44 from the 17-item PCL-S. Dust cloud exposure was dichotomously classified, with “intense” defined as having been in the dust cloud on September 11, 2001, and reporting at least one of the following experiences: unable to see more than a few feet in front of oneself; difficulty walking or finding one’s way; trouble

finding shelter; covered with dust from head to toe; and unable to hear anything. Primary time-to-event analyses used Cox proportional hazards regression to calculate HRs, adjusting for age on September 11, 2001, smoking status (recorded at the wave that preceded stroke hospitalization or at the last completed wave for those without stroke), self-report of physician-diagnosed hypertension or diabetes, sex, race/ethnicity, education, marital status, and eligibility group. A secondary analysis used multinomial logistic regression to examine the association between the number of stroke events (0, 1, and 2 or more) and potential predictors of stroke (PTSD and dust cloud exposure). In the secondary analysis, both stroke subtypes were combined.

Study participants were mostly male (62.6%), Non-Hispanic White (66.4%), and never-smokers (57.5%). There were 475 patients with at least one stroke hospitalization, with 366 classified as ischemic (77%) and 109 (23%) as hemorrhagic. In a smaller sample (n = 27,439) with complete information on covariates, ischemic stroke risk was modestly increased with dust exposure (intense vs minimal or none), but confidence intervals included unity (HR = 1.20; 95% CI: 0.96, 1.50; n = 348). The risk of ischemic stroke did not differ between rescue/recovery workers and other enrollees (i.e., lower Manhattan residents, area workers, or passers–by on the morning of September 11, 2001, and school students/staff on September 11, 2001) (HR = 0.97; 95% CI: 0.76, 1.23). There was no evidence of increased hemorrhagic stroke risk from dust cloud exposure in a similar analysis of 27,194 participants (HR = 0.87; 95% CI: 0.57, 1.32; n = 103). Hemorrhagic stroke risk also did not differ by enrollee type (other enrollees versus rescue/recovery workers, HR = 1.18; 95% CI: 0.76, 1.82). *See* **Table 7**.

PTSD status was significantly associated with both stroke subtypes, as was higher age, being non-Hispanic Black, or being a current smoker. In multinomial logistic regression analyses of the number of stroke hospitalizations per enrollee, PTSD was significantly associated with having one, or two or more strokes, compared to having zero strokes. Dust cloud exposure was significantly associated with having one stroke (OR = 1.33; 95% CI: 1.08, 1.65), but not two or more strokes. *See* **Table 8**.

The study examined WTCHR enrollees including responders and survivors. Study findings suggested an association between 9/11 exposure and stroke although estimates using time-to-event data were largely imprecise. This is the first study to examine stroke subtypes, with findings suggesting a potential non-significant association between 9/11 exposure and ischemic stroke but not hemorrhagic stroke. The study supported the association between PTSD and self-reported stroke described in the earlier study [Yu et al. 2018]. Adding to the previous findings, Yu et al. [2021] observed associations between PTSD and both ischemic and hemorrhagic stroke. The effects of PTSD on stroke risk were stronger than those for dust cloud exposure in models examining both predictors jointly. This finding points to the importance of appropriate control for joint effects

from PTSD and dust exposure. The study raises questions on whether PTSD modifies, mediates, or confounds the association between 9/11 exposure and stroke.

Models examining dust cloud exposure indicated a modest association with ischemic stroke that was similar in magnitude to the association observed in the previous study for both stroke subtypes combined; however, the estimate in the current study was not statistically significant. Notably, the current study is smaller in size, which may explain some loss of estimate precision. The current study also reported significantly positive associations between stroke and several stroke risk factors such as being male, older age, being non-Hispanic Black, being a smoker, and having a history of hypertension. These associations were consistent with the literature and generally stronger than those observed for dust cloud exposure, pointing to the complex etiology and the potential for estimate error by incomplete covariate control.

Overall, Yu et al. [2021] is among the most informative on stroke in the 9/11-exposed population. Notable strengths include a longitudinal design of stroke incidence, objective ascertainment of stroke using hospitalization information, separate analysis of ischemic and hemorrhagic stroke, large sample size including responders and survivors, and long length of follow-up. Many of these strengths addressed important weaknesses discussed in the 2019 evaluation of stroke. However, some important limitations remain. WTCHR studies rely on recruitment and continued retention of participants over the course of the study. Although the WTCHR cohort is large, it is a sample from a much larger exposed population of approximately 400,000 persons. Therefore, there is a potential for effects from recruitment bias. Similarly, losses to follow-up over multiple Waves, including persons who may be debilitated by stroke, is another potential source of information bias. Nonetheless, Yu et al. [2021] conducted post-hoc analyses that included 14,260 Wave 2 nonrespondents, which did not appreciably change results, suggesting that a strong bias from loss to follow-up was unlikely. Finally, although ischemic and hemorrhagic stroke share many risk factors, the authors did not report findings whereby these two outcomes and all stroke counts were combined.

f. Mueller et al. [2024]

Mueller et al. [2024] conducted a cross-sectional study examining CAD and stroke prevalence in male FDNY firefighters who experienced WTC exposures. For stroke (n = 219 FDNY cases), the study examined the odds of self-reported health professional-diagnosis of stroke, cardiovascular accident, or TIA combined among male FDNY firefighters (n = 9,789) in three exposure categories (low, moderate, high) with the odds found among a control group that consisted of other career firefighters (n = 2,729) employed in departments in Chicago, Philadelphia, and San Francisco (i.e., not 9/11-exposed). Self-reported exposure was based on time of arrival at the WTC site.

Self-reported stroke was ascertained using multiple questionnaires for the exposed group (since the question asked to the exposed group was about experiencing stroke in the previous 12 months, all prior FDNY questionnaire information from September 12, 2001, through May 26, 2021, was used to identify stroke prevalence) and a single questionnaire for the control group (which asked about ever having a stroke). ORs were calculated using multivariable logistic regression adjusting for age, race, and BMI in Model 1 and with additional adjustments for high cholesterol, diabetes, hypertension, and smoking status in Model 2. The study also conducted internal exposure-response analysis restricted to FDNY firefighters. Given the availability of medical records for FDNY, internal comparisons were made using cases confirmed by medical record review. Overall, Mueller et al. [2024] found no evidence of exposure-related stroke in external comparisons for Model 1 or Model 2. *See* **Table 9**. In internal comparisons, the OR in the highest exposure category was modestly increased (OR = 1.62; 95% CI: 0.95, 2.77) when using confirmed cases, although the estimate was not statistically significant. *See* **Table 10**. There was little evidence of a positive exposure-response trend (p = 0.10). Both association and trend largely disappeared when using self-reported cases. Interestingly, this pattern was reversed for CAD, where the strength of association and exposure-response trend diminished in models using chart-confirmed cases. None of the findings in this study controlled for PTSD status.

Comparing ascertainment methods (self-report vs. medical record confirmation), the positive predicted value (PPV) and sensitivity for self-reported stroke were 37% and 73%, respectively, suggesting substantial ascertainment error. The cross-sectional design provided limited information on the temporality of the association. In addition, bias from differences in information collection methods between FDNY and control groups cannot be ruled out.

A strength of the study was using other career firefighters as controls; therefore, reducing the potential for bias from healthy worker effects commonly found when comparing a working population with the general population. However, differences remain between FDNY and non-FDNY firefighters that may still lead to selection bias. For example, FDNY firefighters undergo annual physical exams and are likely to be enrolled in the WTC Health Program; therefore, access to healthcare and health awareness are likely improved in FDNY firefighters compared with other firefighters. There were other notable limitations. First, there were group differences in methods of collecting study information, such as the instrument used and the frequency of collection. These differences can potentially lead to biased estimates in group comparisons. Second, internal analyses of FDNY firefighters using self-reported case status with and without medical confirmation showed strengthening of exposure-related effects with stroke following case confirmation; therefore, ascertainment bias cannot be ruled out. Third, the strength of the association was relatively small

for all outcomes tested; therefore, risk estimates are particularly vulnerable to potential biases. Fourth, the cross-sectional design used by this study is generally considered to be minimally informative on causal association. Steps taken to address certain biases or limitations inherent to cross-sectional studies were not described; therefore, interpretation of study findings merits additional caution.

IX. SYNTHESIS OF EVIDENCE FOR CATEGORIZATION

In accordance with the *Policy and Procedures* [NIOSH 2026a], the Science Team evaluates and synthesizes evidence from the high-quality studies identified following the literature review and from the medical basis provided by the petitioners. Synthesis refers to the process by which the Science Team evaluates the evidence presented in scientific studies, individually and together, to characterize the evidence of a causal association between 9/11 exposures and the health condition of interest[50] and to assign findings regarding causal association to one of five categories[51] as described in Section IX.A.4. This evaluation includes a consideration of a weight-of-the-evidence framework commonly referred to as the "Bradford Hill criteria," limitations, and representativeness of the findings.

A. Introduction

1. Bradford Hill Framework for Weight-of-the-Evidence Determinations

The *Policy and Procedures* [NIOSH 2026a] utilizes the Bradford Hill criteria to determine the degree to which the weight of evidence presented by high-quality peer-reviewed, published, epidemiologic studies supports a causal association between 9/11 exposures and the health condition.

The Bradford Hill criteria include: (1) **strength of the association** between 9/11 exposures and the health condition under consideration and precision of the risk estimate; (2) **consistency of associations** across multiple studies; (3) **specificity** that an association is more likely to be causal if one cause (9/11 exposures) and one effect (stroke) is observed; (4) **temporality** of the cause and effect, that is 9/11 exposure precedes the health condition (stroke); (5) **biological gradient** or dose-response relationship where changes in 9/11 exposures are associated with corresponding changes in the magnitude of the outcome (stroke); (6) **biological plausibility** — the extent to which 9/11 studies align with known facts about the biology of the health condition being evaluated (stroke); (7) **coherence** between a causal association and known disease etiology; and (8) **analogy** with an established similar causal relationship [Hill 1965].

Four Bradford Hill criteria — strength of the association, consistency of associations, temporality, and biological gradient — are directly applicable to the evaluation of evidence from high-quality studies identified in the scientific literature review. Each of these four criteria is given significant weight in synthesizing evidence from high-quality studies found after a review of the scientific literature. In contrast, the Bradford Hill criterion of specificity is given no weight due to the multiple causes that can lead to stroke.

50 *See Policy and Procedures*, Section IV.A. [NIOSH 2026a].
51 *Id.* at Section V. [NIOSH 2026a].

Biological plausibility, coherence, and analogy are related criteria that require reasonable knowledge of the biology of the health condition of interest, including facts about disease etiology and any established direct or analogous causal relationships. Although previous biological evidence may have motivated the high-quality epidemiologic studies identified for evaluation, these studies themselves may not provide sufficient information to evaluate the criteria of biological plausibility, coherence, and analogy. To address any concerns regarding incomplete information in the identified studies, the Science Team exercises scientific and medical judgment to refer to additional information from biological, toxicologic, and epidemiologic research, usually from references cited in the identified studies or medical basis studies, or from an additional, limited review of the literature to assess biological plausibility, coherence, and analogy. This approach permits a more complete analysis of these criteria, offsetting the likelihood of reaching a default decision that there is inadequate information to evaluate the likelihood of a causal association.

2. **Study Limitations**

In synthesizing evidence from high-quality studies, the Science Team considers limitations that may affect the validity of study findings. Limitations may include the potential for residual confounding of effect measures from incomplete information on risk factors and major sources of selection or information biases, such as healthy worker effects, adequacy of the control group, ascertainment errors, exposure misclassification, and conflicts of interest, among others. Study limitations are integral to assessing aspects of association, such as strength of the association, consistency of associations, temporality, and biological gradient. For example, large effects (i.e., strength of the association) are generally less vulnerable to study biases. Likewise, cross-sectional studies, by design, generally offer little information on temporality compared with longitudinal studies.

3. **Study Representativeness**

In synthesizing evidence from high-quality studies, the Science Team considers the representativeness of the evidence to assess whether the high-quality studies, taken together, represent both WTC responder and survivor populations or, if only a subgroup of 9/11-exposed responder or survivor populations is represented. If the 9/11-exposed population is only partially represented, then the Science Team considers whether the results can reasonably be extrapolated to the full 9/11-exposed population. Representativeness is linked to consistency of associations such that similar findings observed in multiple populations are generally weighted more heavily than findings observed in a single population.

Due to the interrelatedness of certain Bradford Hill criteria (e.g., strength of the association, consistency of associations, temporality, and biological gradient) and consideration of study limitations and representativeness, those respective criteria may be grouped together for the purpose of synthesizing evidence from the totality of high-quality studies.

The evaluation and synthesis of the evidence from high-quality studies is provided in two parts: (1) consideration of the strength of the association, consistency of associations, temporality, and biological gradient in the identified high-quality studies, including an assessment of study limitations and representativeness of study populations; and (2) consideration of biological plausibility, coherence, and analogy that combines information from the identified high-quality studies with additional information. A summary of the evaluation and synthesis of high-quality studies is provided in Section IX.B. and C. *See* **Table 11**.

4. Categorization of Evidence

After evaluation of the totality of the evidence from high-quality studies, the Science Team categorizes the totality of the evidence into the following five categories: (1) Category I — the evidence supports *substantial likelihood* of a causal association; (2) Category II — the evidence supports the *high likelihood* of a causal association; (3) Category III — the evidence supports a *limited likelihood* of a causal association; (4) Category IV — the evidence *does not support a causal association*; or (5) Category V — the evidence is *inadequate* to determine the likelihood of a causal association [NIOSH 2026a].

This categorization of the evidence is used by the Administrator to determine if there is sufficient evidence of a causal association to conclude that 9/11 exposures are *substantially likely* to be causally associated with the health condition. If categorization of the evidence demonstrates a high, but not substantial, likelihood of causal association between 9/11 exposures and the health condition (Category II), the Administrator may direct the Science Team to evaluate additional highly-relevant scientific information regarding exposures to known 9/11 agents in *non-9/11 exposure scenarios*. Based on such information, coupled with evidence from the evaluation of high-quality studies of the health condition in 9/11-exposed populations, the Science Team will determine whether the totality of the evidence supports a causal association as either Category I (*substantial likelihood*) or Category II (*high likelihood*).

B. Evaluation and Synthesis of High-Quality Studies

1. Consideration of the Strength of the Association, Consistency of Associations, Temporality, and Biological Gradient

There were four previously reviewed studies [Brackbill et al. 2006; Jordan et al. 2013; Remch et al. 2018; Yu et al. 2018]. Of these, one study was cross-sectional [Brackbill et al. 2006] and was not considered further given evidence from more recent longitudinal studies [Yu et al. 2018; Yu et al. 2021]. Details about these studies are provided elsewhere.[52]

Briefly, findings from these previously reviewed studies were inconsistent, and most did not assess the potential for a biological gradient. The limitations and inconsistencies among these studies precluded sufficient evidence supporting a previous petition to add stroke to the List. The previous evaluation found that the evidence from these studies could not adequately

52 *See supra*, note 2

demonstrate that 9/11 exposures were either substantially likely or highly likely to be causally associated with stroke.

New research that examined the association between 9/11 exposures and stroke can be found in six papers published since 2019 [Cohen et al. 2019; Colbeth et al. 2020; Alper et al. 2021; Sloan et al. 2021; Yu et al. 2021; Mueller et al. 2024]. Of these recent studies, the large study of ischemic and hemorrhagic stroke in WTCHR rescue/recovery workers and community members was most informative [Yu et al. 2021]. The researchers addressed many of the concerns of the previous study [Yu et al. 2018] that were raised in the Science Team's evaluation of **Petition 020**. Based on 348 events, the study provided limited evidence of a modest association between WTC-dust exposure and ischemic stroke after adjustment for several risk factors, including PTSD (HR = 1.20; 95% CI: 0.96, 1.50). Modest effects were also observed in two recent studies that examined stroke both as a self-reported outcome and objectively confirmed [Alper et al. 2021; Mueller et al. 2024]. Alper conducted a longitudinal study of WTCHR enrollees and found SPARCS-confirmed stroke to be modestly but non-significantly associated with dust cloud exposure (OR = 1.3; 95% CI: 0.9. 1.7) and being injured on 9/11 (OR = 1.1; 95% CI: 0.7, 1.6). A recent cross-sectional study of chart-confirmed stroke in FDNY firefighters also found a non-significantly elevated risk associated with arrival at the WTC site on the morning of 9/11 (OR = 1.62; 95% CI: 0.95, 2.77) [Mueller et al. 2024]. However, the stroke-related estimates in Alper et al. [2021] and Mueller et al. [2024] varied markedly by ascertainment method; and by modeling in Mueller et al. [2024]. Additionally, the cross-sectional design in Mueller et al. [2024] is much less informative on a causal association compared with estimates from longitudinal studies. In summary, these three studies [Alper et al. 2021; Yu et al. 2021; Mueller et al. 2024] provided some evidence of a causal association between 9/11 exposure and stroke stemming from imprecise estimates of small effects that are most vulnerable to bias. Therefore, evidence of a causal association is limited.

Among other high-quality studies published since 2019, one was a longitudinal design examining mortality patterns in 9/11-exposed responder populations [Colbeth et al. 2020]. Colbeth et al. [2020] found no evidence of excess CeVD mortality in FDNY firefighters. This study restricted relevant analyses to comparisons with an external referent population (i.e., the U.S. general population). This external comparison revealed no evidence of increased risk of mortality from CeVD in the 9/11-exposed population (i.e., all SMRs were less than 1.0). External comparisons in occupational cohorts are vulnerable to selection bias and underestimation of risk. The Science Team concluded that findings from this study were insufficient to support any conclusion of a causal association between 9/11 exposure and stroke.

The two remaining studies did not conduct cause-specific analysis of stroke; however, stroke events were included in composites of CVD [Cohen et al. 2019; Sloan et al. 2021]. Medical confirmation of CVD outcomes was obtained in one study [Cohen et al. 2019], while the other study relied on self-report of a physician diagnosis [Sloan et al. 2021]. These studies found modest, but statistically significant increases in CVD risk among the highest exposed groups (exposure was dichotomized in both studies). However, IHD was the

leading contributor to CVD events in both studies, with stroke contributing much smaller numbers. For example, in the study of CVD risks in FDNY firefighters, there were only 61 "cerebrovascular accidents" included in a composite of 489 primary outcome events, with the remainder categorized as IHD [Cohen et al. 2019]. Likewise, the study of CVD in the GRC reported 670 post-9/11 strokes among 2,385 CVD events [Sloan et al. 2021], compared to 1,441 CAD events, the leading CVD outcome. Overall, a common weakness of these studies is the lack of cause-specific analyses. Based on small numbers, modest effects, and potentially large differences in etiology and physiopathology within the composite, the Science Team concluded that findings from these studies do not adequately inform on the risk of stroke from 9/11 exposure.

In summary, findings across studies were inconsistent. Considered most informative, Yu et al. [2021] reported a modest but imprecise estimate of an association between self-reported WTC-dust exposure and objectively-measured ischemic stroke hospitalization in a large group of WTCHR enrollees. That study controlled for several known risk factors, including PTSD status. In contrast, mortality findings, which consistently indicated attenuated risk [Colbeth et al. 2020], were considered least informative because of a strong potential for selection bias and limited control for risk factors.

2. Study Limitations

Important sources of uncertainty common to more than one study, included four sources. First, studies that examined a group of related health conditions (e.g., all CeVD or all CVD) that included stroke. There is large uncertainty in assuming an association with the composite outcome is an adequate representation of an association with each distinctly different health condition within the composite. Instead, the risk estimate is more likely to indicate the association of the largest contributing outcome or the outcome with the strongest effect (in either direction).

Second, many studies derived health status from self-reported information. There is uncertainty in using self-reported outcome data. Efforts to validate these data or to determine the extent of potential bias from misclassification were assessed in two studies [Alper et al. 2021; Mueller et al. 2024]. One relevant study ascertained cases by self-reported stroke and hospitalization (i.e., SPARCS) data [Alper et al. 2021]. The other study ascertained cases by self-reported stroke and chart-review [Mueller et al. 2024]. Both studies reported estimates for stroke that were largely dependent on the ascertainment method used.

Third, all studies defined categories of 9/11 exposure from self-reported information. Exposure misclassification is likely and may have distorted risk estimates. There were no reports of validating classifications or bias assessments examining the extent of potential bias from exposure misclassification.

Fourth, several studies did not control for PTSD status, which is a potentially important risk factor for stroke in the 9/11-exposed population. Among the

four high-quality studies that assessed stroke as the specific outcome [Yu et al. 2018; Alper et al. 2021; Yu et al. 2021; Mueller et al. 2024] only the two studies by Yu et al. [2018, 2021] controlled for PTSD status. The potential for residual confounding from unmeasured risk factors, such as PTSD, cannot be ruled out.

Fifth, as explained in Section V. of this evaluation, stroke is classified as ischemic or hemorrhagic. However, the Science Team is aware of only one study that examined each of those two types of stroke, and their association with 9/11 exposures, separately [Yu et al. 2021]. The other eight high-quality studies reviewed in this evaluation examined a composite outcome variable. Three of those eight studies combined both stroke types into a single outcome variable [Yu et al. 2018; Alper et al. 2021; Mueller et al. 2024]. Two of those eight studies assessed a composite outcome that consisted of CeVD, which included both types of stroke together with other types of CeVD [Jordan et al. 2013; Colbeth et al. 2020]. Finally, three of the eight studies assessed a broad composite outcome that included various types of CVD, including both types of stroke [Remch et al. 2018; Cohen et al. 2019; Sloan et al. 2021]. In all eight of these other high-quality studies, it is uncertain whether associations observed for the composite outcome are representative of associations with ischemic or hemorrhagic stroke.

3. Study Representativeness

As explained in Section IX.A.3., the Science Team assessed whether the nine high-quality studies, taken together, represent both WTC responder and survivor populations. Among the nine high-quality studies, three included only FDNY responders [Cohen et al. 2019; Colbeth et al. 2020; Mueller et al. 2024]. Two other studies included only GRC responders [Remch et al. 2018; Sloan et al. 2021]. The other four studies included both responders and survivors enrolled in the WTCHR [Jordan et al. 2013; Alper et al. 2021; Yu et al. 2018; Yu et al. 2021].

All nine high-quality studies included only those who were exposed in the NYC disaster area (as defined in 42 C.F.R. § 88.1). Although the Science Team is unaware of any stroke studies involving responders at the Pentagon site, or Shanksville, Pennsylvania site, the Science Team believes it is reasonable to assume that their 9/11-related stroke risks would not differ from responders in the NYC disaster area. As such, the Science Team concluded that there was sufficient representation of all groups of 9/11-exposed populations.

4. Consideration of Biological Plausibility, Coherence, and Analogy

The 9/11-exposed population encountered a dust cloud comprising mostly large particles in an alkaline (pH 9.0 to 11.0) matrix [Landrigan et al. 2004]. Exposures to the dust cloud and to resuspended settled dust posed an inhalation risk somewhat analogous to particulate air pollution, although there is considerable uncertainty given contrasts in exposure scenarios. There is emerging evidence linking long- and short-term ambient particulate air pollution to cerebrovascular events, including both ischemic and hemorrhagic stroke [Stafoggia et al. 2014; Newby et al. 2015; Shah et al. 2015; Rajagopalan

et al. 2018; de Bont et al. 2023]. Although mechanisms remain unclear, it is generally believed that particulate exposures can increase carotid atherosclerosis. In addition, studies have suggested that exposures to air pollution can result in vasoconstriction, hypertension, ischemia, and risk of thrombosis [Shah et al. 2015; Rajagopalan et al. 2018]. Overall, the Science Team concluded that the evidence sufficiently supported the plausibility of a causal association between 9/11 exposure and stroke.

C. Summary of Evaluation and Evidence Synthesis

The evaluation and synthesis of the evidence included an assessment of the strength of the association, consistency of associations, specificity, temporality, and biological gradient based on information in the nine identified high-quality studies, and an assessment of plausibility, coherence, and analogy based on information from the identified high-quality studies from the review of the literature and supplemental studies evaluated for **Petition 020** [Jordan et al. 2013; Remch et al. 2018; Yu et al. 2018]. There was representation of all groups of 9/11-exposed populations. *See* **Table 11**.

X. CONCLUSION

Based on the totality of evidence from eligible studies, the Science Team concludes that a causal association between 9/11 exposures and stroke (ICD 10 codes I60, I61, I63, I64, and G45) is plausible. There was evidence from one informative longitudinal study supporting a modest causal association between 9/11 exposure and ischemic stroke, although the estimate of excess risk was not statistically significant [Yu et al. 2021]. This study was an update of a previous study [Yu et al. 2018] that found a significant association between self-reported stroke and 9/11 dust cloud exposure; however, the update supplanted the previous study's self-reported outcome with documented stroke hospitalizations. There was supporting evidence from other studies showing positive associations between 9/11 exposures and CVD outcomes including stroke. Only one study specifically examined hemorrhagic stroke risk and found no evidence of increased risk [Yu et al. 2021].

Overall, however, the evidence from available epidemiologic studies lacked sufficient consistency of associations and precision to eliminate alternative explanations of the association, such as bias, confounding, or chance. Therefore, the Science Team concludes that the current evidence is insufficient to support a finding of *substantial* or *high likelihood* of a causal association. Based on weight of evidence, the Science Team concludes that: (1) the available evidence of a causal association between 9/11 exposures and ischemic stroke is *limited*;[53] and (2) the available evidence of a causal association between 9/11 exposures and hemorrhagic stroke or a transient ischemic attack is *inadequate*.[54]

53 *See Policy and Procedures*, Section V.C. [NIOSH 2026a].
54 *See Policy and Procedures*, Section V.E. [NIOSH 2026a].

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Yu S, Alper HE, Nguyen AM, et al. [2021]. Stroke hospitalizations, posttraumatic stress disorder, and 9/11-related dust exposure: Results from the World Trade Center Health Registry. Am J Ind Med *64*(10):827–836, https://doi.org/10.1002/ajim.23271.

APPENDIX — TABLES

Table 1a. Medical Basis Information Provided by Current Petitioners.

Petition Number	Information Provided in Each Petition	Medical Basis[1] (Yes/No)
Petition 048	1. Jordan HT, Miller-Archie SA, Cone JE, et al. [2011b]. Heart disease among adults exposed to the September 11, 2001 World Trade Center disaster: results from the World Trade Center Health Registry. Prev Med *53*(6):370–376, https://doi.org/10.1016/j.ypmed.2011.10.014	No
	2. Jordan HT, Stellman SD, Morabia A, et al. [2013]. Cardiovascular disease hospitalizations in relation to exposure to the September 11, 2001 World Trade Center disaster and posttraumatic stress disorder. J Am Heart Assoc *2*(5):e000431, https://doi.org/10.1161/JAHA.113.000431	No
	3. Brackbill RM, Cone JE, Farfel MR, Stellman SD [2014]. Chronic physical health consequences of being injured during the terrorist attacks on World Trade Center on September 11, 2001. Am J Epidemiol *179*(9):1076–1085, https://doi.org/10.1093/aje/kwu022	No
	4. Alper HE, Yu S, Stellman SD, Brackbill RM [2017]. Injury, intense dust exposure, and chronic disease among survivors of the World Trade Center terrorist attacks of September 11, 2001. Injury epidemiology *4*(1):17, https://doi.org/10.1186/s40621-017-0115-x	No
	5. Cohen HW, Zeig-Owens R, Joe C, et al. [2019]. Long-term cardiovascular disease risk among firefighters after the World Trade Center disaster. JAMA Network Open *2*(9):e199775–e199775, https://doi.org/10.1001/jamanetworkopen.2019.9775	Yes
	6. Sloan NL, Shapiro MZ, Sabra A, et al. [2021]. Cardiovascular disease in the World Trade Center Health Program General Responder Cohort. Am J Ind Med *64*(2):97–107, https://doi.org/10.1002/ajim.23207	Yes
	7. Jordan HT, Stein CR, Li J, et al. [2018]. Mortality among rescue and recovery workers and community members exposed to the September 11, 2001 World Trade Center terrorist attacks, 2003-2014. Environ Res *163*:270–279, https://doi.org/10.1016/j.envres.2018.01.004.	No

Petition Number	Information Provided in Each Petition	Medical Basis[1] (Yes/No)
Petition 048 (cont.)	8. Li J, Hall CB, Yung J, et al. [2023]. A 15-year follow-up study of mortality in a pooled cohort of World Trade Center rescue and recovery workers. Environ Res *219*:115116, https://doi.org/10.1016/j.envres.2022.115116	No
	9. Brook RD, Rajagopalan S, Pope CA, 3rd, et al. [2010]. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation *121*(21):2331–-2378, https://doi.org/10.1161/CIR.0b013e3181dbece1	Yes
	10. Newby DE, Mannucci PM, Tell GS, et al. [2015]. Expert position paper on air pollution and cardiovascular disease. Eur Heart J *36*:83–93, https://doi.org/10.1093/eurheartj/ehu458	Yes
	11. Kaufman JD, Adar SD, Barr RG, et al. [2016]. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. Lancet *388*(10045):696–704, https://doi.org/10.1016/S0140-6736(16)00378-0	No
	12. Yu S, Alper HE, Nguyen AM, Maqsood J, Brackbill RM [2021]. Stroke hospitalizations, posttraumatic stress disorder, and 9/11-related dust exposure: Results from the World Trade Center Health Registry. Am J Ind Med *64*(10):827–836, https://doi.org/10.1002/ajim.23271	Yes
	13. Yu S, Alper HE, Nguyen AM, Brackbill RM [2018]. Risk of stroke among survivors of the September 11, 2001, World Trade Center disaster. J Occup Environ Med *60*(8):e371–e376, https://doi.org/10.1097/JOM.0000000000001361	No
	14. Remch M, Laskaris Z, Flory J, et al. [2018]. Post-traumatic stress disorder and cardiovascular diseases: A cohort study of men and women involved in cleaning the debris of the World Trade Center complex. Circ Cardiovasc Qual Outcomes *11*(7):e004572, https://doi.org/10.1161/CIRCOUTCOMES.117.004572	No
	15. Wanahita N, See JL, Giedd KN, et al. [2010]. No evidence of increased prevalence of premature coronary artery disease in New York City police officers as predicted by coronary artery calcium scoring. J Occup Environ Med *52*(6):661–665, https://doi.org/10.1097/JOM.0b013e3181e36457	No

Petition Number	Information Provided in Each Petition	Medical Basis[1] (Yes/No)
Petition 048 (cont.)	16. Lioy PJ, Weisel CP, Millette JR, et al. [2002]. Characterization of the dust/smoke aerosol that settled east of the World Trade Center in lower Manhattan after the collapse of the WTC 11 September 2001. Environ Health Perspect *110*(7):703–714, https://pubmed.ncbi.nlm.nih.gov/12117648/	No
	17. Newman JD, Bhatt DL, Rajagopalan S, et al. [2020]. Cardiopulmonary impact of particulate air pollution in high-risk populations: JACC state-of-the-art review. J Am Coll Cardiol *76*(24):2878–2894, https://doi.org/10.1016/j.jacc.2020.10.020	Yes
	18. McGuinn L, Schneider A, McGarrah R, et al. [2019]. Association of long-term PM2.5 exposure with traditional and novel lipid biomarkers related to cardiovascular disease risk. Environ Int *122*:193–200, https://doi.org/10.1016/j.envint.2018.11.001	No
	19. Ghio A, Soukup J, Madden M [2018]. The toxicology of air pollution predicts its epidemiology. Inhal Toxicol *30*(9–10):327–334, https://doi.org/10.1080/08958378.2018.1530316	No
	20. Ward-Caviness C [2019]. A review of gene-by-air pollution interactions for cardiovascular disease, risk factors, and biomarkers. Hum Genet *138*(6):547–561, https://doi.org/10.1007/s00439-019-02004-w	No
	21. Cascio W, Long T [2018]. Ambient air quality and cardiovascular health: Translation of environmental research for public health and clinical care. N C Med J *79*(5):306–312, https://doi.org/10.18043/ncm.79.5.306	Yes
	22. Devlin R, Bailey Smith C, Schmitt MT, et al. [2014]. Controlled exposure of humans with metabolic syndrome to concentrated ultrafine ambient particulate matter causes cardiovascular effects. Toxicol Sci *140*(1):61–72, https://doi.org/10.1093/toxsci/kfu063	No
	23. Jhun I, Kim J, Cho B, et al. [2019]. Synthesis of Harvard Environmental Protection Agency (EPA) Center studies on traffic-related particulate pollution and cardiovascular outcomes in the Greater Boston Area. J Air Waste Manag Assoc *69*(8):900–917, https://doi.org/10.1080/10962247.2019.1596994	No

Petition Number	Information Provided in Each Petition	Medical Basis[1] (Yes/No)
Petition 048 (cont.)	24. Cohen AJ, Brauer M, Burnett R, et al. [2017]. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015. Lancet *389*(10082):1907–1918, https://doi.org/10.1016/S0140-6736(17)30505-6	Yes
	25. Thurston GD, Kipen H, Annesi-Maesano I, et al. [2017]. A joint ERS/ATS policy statement: What constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J *49*:1600419, https://doi.org/10.1183/13993003.00419-2016	Yes
	26. Shanley RP, Hayes RB, Cromar KR, et al. [2016]. Particulate air pollution and clinical cardiovascular disease risk factors. Epidemiology *27*(2):291–298, https://pubmed.ncbi.nlm.nih.gov/26605815/	No
	27. Serra R, Abramo A, Ielapi N, et al. [2021]. Environmental pollution and peripheral artery disease. Risk Manag Healthc Policy *14*:2181–2190, https://doi.org/10.2147/RMHP.S307150	No
	28. O'Donnell CJ, Schwartz Longacre L, Cohen BE, et al. [2021]. Posttraumatic stress disorder and cardiovascular disease: State of the science, knowledge gaps, and research opportunities. JAMA Cardiol *6*(10):1207–1216, https://doi.org/10.1001/jamacardio.2021.2530	No
	29. Edmondson D, von Känel R [2017]. Post-traumatic stress disorder and cardiovascular disease. Lancet Psychiatry *4*(4):320–329, https://doi.org/10.1016/S2215-0366(16)30377-7	No
	30. Hargrave AS, Sumner JA, Ebrahimi R, Cohen BE [2022]. Posttraumatic stress disorder (PTSD) as a risk factor for cardiovascular disease: Implications for future research and clinical care. Curr Cardiol Rep *24*(12):2067–2079. https://doi.org/10.1007/s11886-022-01809-y	No
	31. Scherrer JF, Salas J, Schneider FD, et al. [2020]. PTSD improvement and incident cardiovascular disease in more than 1000 veterans. J Psychosom Res *134*:110128. https://doi.org/10.1016/j.jpsychores.2020.110128	No

Petition Number	Information Provided in Each Petition	Medical Basis[1] (Yes/No)
Petition 048 (cont.)	32. EPA [2019]. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019). Washington, DC: Environmental Protection Agency, EPA/600/R-19/188, https://hero.epa.gov/reference/6591812/.	Yes
	33. Beristianos MH, Yaffe K, Cohen B, Byers AL [2016]. PTSD and risk of incident cardiovascular disease in aging veterans. Am J Geriatr Psychiatry *24*(3):192–200. https://doi.org/10.1016/j.jagp.2014.12.003	No
Petition 051a	1. Cohen HW, Zeig-Owens R, Joe C, et al. [2019]. Long-term cardiovascular disease risk among firefighters after the World Trade Center disaster. JAMA Network Open *2*(9):e199775–e199775, https://doi.org/10.1001/jamanetworkopen.2019.9775	Yes
	2. Sloan NL, Shapiro MZ, Sabra A, et al. [2021]. Cardiovascular disease in the World Trade Center Health Program General Responder Cohort. Am J Ind Med *64*(2):97–107, https://doi.org/10.1002/ajim.23207	Yes
	3. Remch M, Laskaris Z, Flory J, et al. [2018]. Post-traumatic stress disorder and cardiovascular diseases: A cohort study of men and women Involved in cleaning the debris of the World Trade Center complex. Circ Cardiovasc Qual Outcomes *11*(7):e004572, https://doi.org/10.1161/CIRCOUTCOMES.117.004572	No
	4. Berry C, Duncker DJ [2020]. Coronary microvascular disease: The next frontier for Cardiovascular Research. Cardiovasc Res *116*(4):737–740, https://doi.org/10.1093/cvr/cvaa035	No

1. Medical basis must be scientific in nature and provide a positive association between the September 11, 2001, terrorist attacks and the condition to be added through peer-reviewed, published literature that has not been previously evaluated by the Program. For more information, please *see* NIOSH [2026b].

Table 1b. Studies that Provided Sufficient Medical Basis Information and Whether They Met High-Quality Study Criteria, by Petition.

	Petition 048	Petition 051a	Met High Quality Study Criteria
Brook et al. [2010]	☑		
Newby et al. [2015]	☑		
Cohen et al. [2017]	☑		
Thurston et al. [2017]	☑		
Cascio and Long [2018]	☑		
Cohen et al. [2019]	☑	☑	☑
EPA [2019]	☑		
Newman et al. [2020]	☑		
Sloan et al. [2021]	☑	☑	☑
Yu et al. [2021]	☑		☑

Table 2. Identified Studies Evaluated by the Science Team from Previous Petitions.

Authors	Follow-up	Population	Endpoint	Characteristics	Confounding Control	Dust Exposure[1]
Brackbill et al [2006]	2003-2004	WTCHR	CAD, angina, MI, stroke; incidence, self-report	cross-sectional; 8,418 adult survivor enrollees occupying damaged of collapsed buildings and completing Wave 1; 54.2% male	angina–age, sex, recruitment mode, race/ethnicity, psychological distress, smoking; CAD and MI–sex, recruitment mode	+
Jordan et al [2013]	2003-2010	WTCHR	CeVD incidence, hospital records based.	longitudinal cohort; 46,346 enrollees; 40.3% female; average age on 9/11 among males 40.7 years	age, sex, race/ethnicity, education, smoking, hypertension, diabetes	-
Mani et al. [2013]	NR	GRC	multi contrast MRI and DCE-MRI, ankle-brachial index	cross-sectional; 31 law enforcement personnel; 10% female	NR	+
Remch et al. [2018]	2012-2016	GRC	CVD (MI, stroke) incidence, self-report	longitudinal cohort; 5,971 general responders enrolled in 2012-2013; 20.8% female; 54% White; mean age: 51 years	age, sex, race/ethnicity, smoking, hypertension, diabetes, BMI	-
Yu et al. [2018]	2003-2016	WTCHR	Stroke incidence, self-report	longitudinal cohort; 42,527 rescue/recovery workers and non-rescue/recovery workers participating in Wave 1 and 2 surveys; 61% male;	age, sex, race/ethnicity, education, marital status, and enrollees' eligibility group, smoking status, hypertension, diabetes, PTSD.	+

1. A plus sign (+) indicates at least one statistically significant positive association and minus sign (-) indicates no significant association.
2. Data collection period for administered questionnaires.

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CeVD, cerebrovascular disease; CVD, cardiovascular disease; DCE-MRI, dynamic contrast enhanced magnetic resonance imaging; GRC, General Responder Cohort; MI, myocardial infarction; MRI; magnetic resonance imaging; PTSD, posttraumatic stress disorder; WTCHR, World Trade Center Health Registry.

Table 3. Identified High-Quality Studies Not Previously Evaluated.

Authors	Follow-up	Population	Endpoint	Characteristics	Confounding Control	Dust Exposure[1]
Cohen et al. [2019]	2001-2017	FDNY	CVD (MI, stroke, unstable angina, coronary artery surgery or angioplasty, congestive heart failure, or CVD death); incidence, records-based	longitudinal cohort: 9,796 male firefighters; average age 40.3 years	sex, race/ethnicity, smoking, cholesterol, hypertension, diabetes, BMI, protective services	+
Colbeth et al. [2020]	2001-2017	FDNY	CeVD mortality, DCERT records-based	longitudinal cohort; 15,431 firefighters and EMS (exposure-response restricted to 15,058); 3.2% female; median age on 9/11: 39.9 years; 87.2% non-Hispanic White	sex, age, race/ethnicity, calendar period	-
Yu et al. [2021]	2003-2016	WTCHR	Stroke (ischemic, hemorrhagic separately) incidence, hospital records-based	longitudinal cohort; 27,439 rescue/recovery workers and non-rescue/recovery workers participating in Wave 1 and 2 surveys, with complete covariate information; 60.5% male	sex, age, race/ethnicity, education, marital status, and enrollees' eligibility group, smoking status, hypertension, diabetes, PTSD	-[2]
Alper et al. [2021]	2002-2015	WTCHR	Stroke prevalence, self-report and records-based	longitudinal cohort; 18,206 rescue/recovery workers who completed Waves 1 through 4, and resided in New York State at Waves 2 and 3; with complete covariate information; 61% male; 51% aged 25–44 on September 11, 2001	sex, age on 9/11, race/ethnicity, and education	+[3]
Sloan et al. [2021]	2002-2019	GRC	CAD, MI, stroke, or CHF combined; self-report	longitudinal cohort; 37,725 responders; 13.7% female; median age 37 years (19-80); 53.7% White	sex, race/ethnicity, smoking, cholesterol, hypertension, diabetes, BMI, PTSD	+

Authors	Follow-up	Population	Endpoint	Characteristics	Confounding Control	Dust Exposure[1]
Mueller et al. [2024]	2019-2021[4]	FDNY	CVD (CAD or stroke), stroke, CAD; prevalence, self-report and records-based	cross-sectional; 9,789 male FDNY firefighters and 2,729 unexposed controls; average age 40.0 years on 9/11; 94.1% non-Hispanic White	age, race/ethnicity, BMI, hypertension, diabetes, smoking	-

1. In longitudinal analyses, a plus sign (+) indicates at least one statistically significant positive association and minus sign (-) indicates no significant association.
2. In cross-sectional analysis, the estimate of an association between dust cloud exposure and having one stroke (ischemic and hemorrhagic stroke was combined in this analysis) was significant, but not for having two or more strokes.
3. Significantly elevated only for the self-reported stroke outcome and not the records-based stroke outcome.
4. Data collection period for administered questionnaires.

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CeVD, cerebrovascular disease; CHF, congestive heart failure; CVD, cardiovascular disease; DCERT, death certificate; FDNY, Fire Department of the City of New York; EMS, emergence medical services; GRC, General Responder Cohort; MI, myocardial infarction; SMR, standardized mortality ratio; PTSD, posttraumatic stress disorder; and WTCHR, World Trade Center Health Registry.

Table 4. Associations of 9/11-exposures with cerebrovascular disease hospitalization among WTCHR enrollees residing in New York State, 2003–2010. Adapted from Jordan et al. [2013].

		Women (*n* = 18,551)		Men (*n* = 27,511)
Exposure	***n***	**aHR[1] (95% CI)**	***n***	**aHR (95% CI)**
9/11 dust cloud exposure (all enrollees)				
Yes	76	0.84 (0.58, 1.22)	85	1.03 (0.75, 1.42)
No	51	Reference	71	Reference
Injured on 9/11 (all enrollees)				
Yes	64	1.31 (0.91, 1.89)	68	1.14 (0.82, 1.57)
No	64	Reference	88	Reference
PTSD at enrollment (all enrollees)				
Yes	37	1.38 (0.92, 2.07)	68	1.53 (1.03, 2.27)
No	87	Reference	121	Reference
Overall level of exposure (rescue/recovery workers)				
High	0	NA	12	1.66 (0.46, 5.95)
Intermediate	14	1.40 (0.31, 6.39)	60	1.33 (0.42, 4.27)
Low	2	Reference	4	Reference
Overall level of exposure (non-rescue/recovery workers)				
High	11	1.22 (0.60, 2.47)	4	0.83 (0.29, 2.36)
Intermediate	60	0.34 (0.87, 2.08)	41	1.16 (0.71, 1.90)
Low	39	Reference	32	Reference

1. Hazard ratios were adjusted for race/ethnicity, education, marital status, smoking, diabetes, and hypertension.

Abbreviations: CI, confidence interval; aHR, adjusted hazard ratio; NA, not applicable; PTSD, posttraumatic stress disorder; WTCHR, World Trade Center Health Registry.

Table 5. Odds ratios for associations between stroke and dust cloud exposure, injuries, traumatic events, and PTSD in WTCHR enrollees, comparing self-report and SPARCS-derived hospitalizations. Adapted from Alper et al. [2021].

Exposure[1]	*n*	Self-report OR (95% CI)[2]	SPARCS OR (95% CI)
Caught in dust cloud	10,262	1.5 (1.2, 1.8)	1.3 (0.9, 1.7)
One or more injuries on 9/11	2,641	1.3 (1.0, 1.6)	1.1 (0.7, 1.6)
Witnessed 3 or more traumatic events	6,823	1.4 (1.1, 1.7)	1.0 (0.8, 1.4)
PTSD	2,666	1.9 (1.5, 2.4)	1.5 (1.1, 2.2)

1. The referent for each category had no exposure to the item in that category.
2. Adjusted for age, race/ethnicity, sex, and education.

Abbreviations: CI, confidence interval; OR, odds ratio; PTSD, post-traumatic stress disorder; SPARCS, New York State Department of Health's Statewide Planning and Research Cooperative System.

Table 6. Associations between 9/11 arrival time/dust cloud exposure and CVD[1] in 37,725 general responders, 2002–2019. Adapted from Sloan et al. [2021].

Exposure	Women (*n* = 5,186) HR[2] (95% CI)	Men (*n* = 32,539) HR (95% CI)
Very High	2.17 (1.50, 3.14)	1.29 (1.16, 1.44)
High	1.49 (1.04, 2.13)	1.33 (1.20, 1.47)
Low/Intermediate	Reference	Reference
After adjusting for protective services employment		
Very High	1.61 (1.10, 2.36)	1.04 (0.93, 1.17)
High	1.18 (0.82, 1.70)	1.16 (1.05, 1.28)
Low/Intermediate	Reference	Reference

1. CVD outcomes include coronary artery disease, myocardial infarction, stroke, and congestive heart failure.
2. Models adjusted for race/ethnicity, smoking, cholesterol, hypertension, diabetes mellitus, and BMI.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

Table 7. Risk of ischemic and hemorrhagic stroke by dust intensity and eligibility group. Adapted from Yu et al. [2021].

	Ischemic stroke or transient ischemic attack (*n* = 348)		Hemorrhagic stroke (*n* = 103)	
	aHR[1]	95% CI	aHR	95% CI
Dust intensity				
Intense	1.20	(0.96, 1.50)	0.87	(0.57, 1.32)
None/minimal	Referent		Referent	
Eligibility group				
Rescue/recovery worker	Referent		Referent	
Other[2]	0.97	(0.76, 1.23)	1.18	(0.76, 1.82)

1. aHR adjusted by age at 9/11/2001, sex, race/ethnicity, education, marital status, and eligibility group.
2. The "other" group consists of lower Manhattan residents, area workers, or passers-by on the morning of 9/11, and school students/staff on 9/11.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

Table 8. Risk of stroke and recurrent strokes by dust intensity and eligibility group. Adapted from Yu et al. [2021].

	0 strokes (*n* = 28,537)	1 stroke (*n* = 396)			≥ 2 strokes (*n* = 79)		
	%	%	aOR[1]	95% CI	%	aOR	95% CI
Dust intensity							
Intense	98.03	1.71	1.33	(1.08, 1.65)	0.26	0.79	(0.48, 1.29)
None/minimal	98.53	1.19	Referent		0.28	Referent	
Eligibility group							
Rescue/recovery worker	98.43	1.30	Referent		0.27	Referent	
Other[2]	98.29	1.43	0.97	(0.77, 1.23)	0.28	1.07	(0.65, 1.77)

1. ORs adjusted by age at 9/11/2001, sex, race/ethnicity, education, marital status, and eligibility group.
2. The "other" group consists of lower Manhattan residents, area workers, or passers-by on the morning of 9/11, and school students/staff on 9/11.

Abbreviations: CI, confidence interval; aOR, adjusted odds ratio.

Table 9. Odds ratios from external comparisons of stroke, comparing FDNY firefighters with non-WTC-exposed firefighters. Adapted from Mueller et al. [2024].

Exposure[1]	Model 1 OR (95% CI)[2]	Model 2 OR (95% CI)[3]
Ever/never	1.03 (0.79, 1.35)	0.93 (0.71, 1.22)
High	1.18 (0.80, 1.75)	1.04 (0.70, 1.55)
Moderate	1.07 (0.79, 1.44)	0.97 (0.72, 1.30)
Low	0.90 (0.64, 1.27)	0.81 (0.57, 1.15)
linear trend	$p = 0.33$	$p = 0.74$

1. Non-WTC-exposed firefighters from Chicago, Philadelphia, and San Francisco, used as the referent group.
2. Model 1, adjusted for age, race, and BMI.
3. Model 2, Adjusted for age, race, BMI, high cholesterol, diabetes, hypertension, smoking (ever/never).

Abbreviations: BMI, body mass index; CI, confidence interval; FDNY, Fire Department of the City of New York; OR, odds ratio; WTC, World Trade Center.

Table 10. Odds ratios[1] from internal comparisons of stroke among FDNY firefighters. Adapted from Mueller et al. [2024].

Exposure[2]	Self-reported OR (95% CI)	Validated OR (95% CI)[3]
High	1.22 (0.81, 1.85)	1.62 (0.95, 2.77)
Moderate	1.18 (0.86, 1.62)	1.06 (0.68, 1.66)
linear trend	$p = 0.29$	$p = 0.10$

1. Models adjusted for age, race, BMI, high cholesterol, hypertension, diabetes, and smoking.
2. Exposure among FDNY firefighters was stratified into three categories with the low exposure category as the referent group.
3. Self-reported case status that was confirmed by medical record review.

Abbreviations: BMI, body mass index; CI, confidence interval; FDNY, Fire Department of the City of New York; OR, odds ratio; WTC, World Trade Center.

Table 11. Summary of Bradford Hill Criteria Used in Evaluation and Evidence Synthesis.

Aspect of Associative Causal Inference	Evaluation Findings
Strength of the Association (and estimate of precision)	Modest positive associations were evident in some studies that were suggestive of a causal association. One earlier study of self-reported stroke reported a modest but statistically significant association with WTC-dust exposure [Yu et al. 2018]. However, statistically significant estimates of exposure-related stroke were not reported by any study published since the evaluation for **Petition 020** was published. Two studies of responders reported significant positive associations between 9/11 exposure and a composite outcome in which cerebrovascular disease was a minor contributor [Cohen et al. 2019; Sloan et al. 2021]. Objective measures of stroke events and stroke risk were limited to three studies published since the previous evaluation [Alper et al. 2021; Yu et al. 2021; Mueller et al. 2024], and none of those studies found significant risk elevations in those objective stroke measures from 9/11 exposures.
Consistency of Associations	Findings among studies were inconsistent, ranging from strong deficits in mortality [Colbeth et al. 2020] to modest, but statistically significant increases in incidence in four studies [Yu et al. 2018; Cohen et el. 2019; Alper et al. 2021; Sloan et al. 2021]. In general, the inconsistency may be attributable to large differences in outcome definition and study designs. For example, large differences in risk estimates were observed in one study using both self-reported stroke and stroke ascertained from medical records [Mueller et al. 2024]. In another study using both self-reported stroke and stroke ascertained from medical records, risk estimates were statistically significant only for self-reported stroke [Alper et al. 2021]. Only one study differentiated between ischemic and hemorrhagic stroke subtypes [Yu et al. 2021]. That study reported a modest but imprecise estimate of an association between 9/11 exposure and ischemic stroke, and no evidence of an association with hemorrhagic stroke. Despite ischemic and hemorrhagic stroke having similar risk factors, Yu et al. [2021] did not report findings for all types of stroke combined.
Temporality	Longitudinal study designs reduced the potential for errors from preexisting conditions. Researchers attempted to exclude persons with previous stroke. However, given potentially long latency, stroke and related health conditions may have manifested prior to 9/11. Analyses examining temporal effects (e.g., latency and persistence) were not conducted.

Aspect of Associative Causal Inference	Evaluation Findings
Biological Gradient	Mueller et al. [2024] was the only study that used a specific stroke outcome and also examined biological gradient. It found evidence suggestive of modestly increasing stroke risk across increasing categories of 9/11 exposure, but the trend was not statistically significant.
Plausibility, Coherence, and Analogy	An association between WTC dust exposure and stoke is coherent with the available evidence. There is large uncertainty in an analogy comparing a proposed causal association between WTC dust exposure and stroke and the possible relationship between $PM_{2.5}$ in air pollution and stroke. The latter is supported by evidence linking long-term exposure to ambient air pollution to increased stroke risk. Chronic exposure to $PM_{2.5}$ in air pollution and acute exposure to WTC dusts are largely dissimilar. There is sparse evidence available on the relevant etiologic period for late cardiovascular effects from $PM_{2.5}$ exposure; therefore, the biological plausibility of these effects remains largely uncertain.
Representativeness	There was representation of all groups of 9/11-exposed populations.