9.11 World Trade Center Health Program

Evaluation of Scientific Evidence Supporting the Addition of Peripheral Artery Disease to the List of WTC-Related Health Conditions

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I. EXECUTIVE SUMMARY

At the direction of the Administrator of the World Trade Center (WTC) Health Program (Administrator), the WTC Health Program's Science Team (Science Team) reviewed one petition — **Petition 048a** — requesting the addition of "peripheral vascular disease" to the List of WTC-Related Health Conditions (the List). The Administrator understands the term "peripheral vascular disease" to mean the health condition known as "peripheral artery disease" (PAD) [Campia et al. 2019]. In a related action, the Administrator previously evaluated a request for "atherosclerosis," an antecedent health condition leading to the development of PAD, in **Petition 012**; the evaluation resulted in a finding of *insufficient evidence* to add atherosclerosis to the List.[1]

The Science Team evaluated the scientific evidence of a causal association between 9/11 exposures and PAD 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 published between September 2001, and June 2026 identified nine studies reporting on the risk of PAD in 9/11-exposed populations.

The Science Team evaluated the information from the nine studies identified in the review of the literature, which included one study identified in the previous literature review conducted for **Petition 012**, individually and together, to characterize the available scientific evidence of a causal association between 9/11 exposures and PAD. Based on the weight of the evidence, the Science Team concludes that there is *inadequate evidence* to determine the likelihood of a causal association between 9/11 exposures and PAD (Category V).[2]

II. BACKGROUND

Pursuant to the James Zadroga 9/11 Health and Compensation Act of 2010,[3] an interested party may petition the Administrator of the WTC Health Program (Program) for the addition of a health condition to the List of conditions eligible for treatment in the Program.[4,5] 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 health condition.[6] 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.

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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 Policy and Procedures*, Section V.E. [NIOSH 2026a].
3 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.
4 42 U.S.C. § 300mm-22(a)(6)(B).
5 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).
6 *See* 42 C.F.R. § 88.16(a)(1).

A. Current Petition 048a

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[7] to separate the scientific evaluation of the eight conditions provided in the submission into three separate Petitions and evaluations:[8] (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). The Administrator directed that the first group of health conditions be evaluated under the category "ischemic heart disease" as **Petition 047**.[9] The Administrator directed that the second health condition, stroke, be evaluated under a new ordinal number as **Petition 048**.[10] The third health condition, PVD, is assessed in the current evaluation under a new ordinal number as **Petition 048a**. The Administrator understands the term "peripheral vascular disease" to mean the health condition commonly known as "peripheral artery disease" (PAD) [Campia et al. 2019].

B. Previous Petition 012

On April 11, 2016, the Administrator received two related submissions, combined into **Petition 012**, to add "atherosclerosis" to the List. 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 the *Federal Register* on December 14, 2016.[11] The findings from this previous evaluation are discussed in Section VIII.B.1. below.

III. PURPOSE

The purpose of this evaluation is to assess the scientific evidence from peer-reviewed, published, epidemiologic studies of PAD in the 9/11-exposed population,[12] to determine whether sufficient evidence of a causal association between 9/11-related exposures, including exposure to 9/11 agents,[13] and PAD exists to support adding the health condition to

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

8 To ensure a comprehensive scientific evaluation of each of the specific health conditions requested in **Petition 047**, 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 10.

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

10 *See* https://www.cdc.gov/niosh/docket/archive/pdfs/niosh-094/WTCHP-Stroke-Scientific-Evaluation.pdf.

11 *See supra*, note 1.

12 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].

13 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].

the List. This evaluation is being provided to the Administrator to inform the Administrator's determination regarding **Petition 048a**, in accordance with the WTC Health Program's *Policy and Procedures* [NIOSH 2026a].

IV. REVIEW OF MEDICAL BASIS INFORMATION PROVIDED BY THE PETITIONER

The validity of **Petition 048a** 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 the submission to determine whether they provided a medical basis for an association between the September 11, 2001, terrorist attacks and the health condition to be added to the List. *See* **Table 1a**. Seven distinct studies provided by the petitioner[14] were determined to provide sufficient medical basis for the petition. *See* **Table 1b**.

A. Petition 048a

As noted above in Section II.A., that portion of **Petition 047** pertaining to the health condition PAD was assigned the ordinal **Petition 048a** and is reviewed herein separately from the other conditions included in **Petition 047**. **Petition 047** provided 33 studies as medical basis. These 33 studies covered several cardiovascular and cerebrovascular health conditions, including myocardial infarction (MI), unstable angina, obstructive coronary artery disease, ischemic cardiomyopathy, ischemic congestive heart failure, arrythmias (due to any of the above), stroke, and PAD. For purposes of **Petition 048a**, those 33 studies provided as medical basis for **Petition 047** were reviewed only for how they pertain to PAD.

Sufficient Medical Basis Studies. Seven of the 33 studies provided sufficient medical basis for PAD [Brook et al. 2010; Newby et al. 2015; Thurston et al. 2017; Cascio and Long 2018; Cohen et al. 2019; EPA 2019; Serra et al. 2021]. Six of the seven studies that provided sufficient medical basis each described increased PAD risks associated with air pollution exposure, including particulate matter (PM) with an aerodynamic diameter ≤ 2.5 micrometers (μm) in diameter ($PM_{2.5}$) [Brook et al. 2010; Newby et al. 2015; Thurston et al. 2017; Cascio and Long 2018; EPA 2019; Serra et al. 2021]. All seven studies are briefly summarized below.

Brook et al. [2010] presented a scientific statement from the American Heart Association (AHA) concluding that modest epidemiologic evidence exists to support an association between $PM_{2.5}$ exposure and increased PAD morbidity.

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 cardiovascular disease (CVD) outcomes including PAD. It identified some studies that found air pollution exposure increased the risk of PAD morbidity and mortality.

14 Although **Petition 048a** had eight signatories, the Science Team uses the singular (i.e., "petitioner") when there is only one petition.

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 and provides references to papers that describe increased risks of impaired vascular function and increased carotid artery stenosis from $PM_{2.5}$ exposure.

Cascio and Long [2018] provided a non-systematic review on the CVD effects, including PAD, from air pollution. The review reported that residential proximity to major roads is associated with increased PAD risk.

Cohen et al. [2019] is a peer-reviewed, published longitudinal cohort study of Fire Department of New York (FDNY) firefighters designed to assess whether 9/11 exposures were associated with elevated CVD risk, including a composite outcome variable. Among firefighters with the composite outcome, very few had PAD, however, the study found positive associations between this composite cardiovascular outcome and 9/11 exposures related to time of arrival and length of response. The study is discussed in Section VIII.B.2.d.

EPA [2019] is a detailed integrated science assessment that examined the impact of PM, including $PM_{2.5}$, on various CVD outcomes, including PAD. The assessment summarized several studies that found increased PAD risk associated with $PM_{2.5}$ exposure.

Serra et al. [2021] provided a review of environmental pollutant exposures associated with PAD. This study provided evidence supporting an association between exposure to PM_{10} and increased PAD risk.

Insufficient Medical Basis Studies. Twenty-six studies submitted with **Petition 048a** did not provide sufficient medical basis for PAD [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; Cohen et al. 2017; Edmondson and von Kanel 2017; Ghio et al. 2018; Jordan et al. 2018; Remch et al. 2018; Yu et al. 2018; McGuinn et al. 2019; Ward-Caviness 2019; Jhun et al. 2019; Newman et al. 2020; Scherrer et al. 2020; O'Donnell et al. 2021; Sloan et al. 2021; Yu et al. 2021; Hargrave et al. 2022; Li et al. 2023]. These 26 studies did not examine the association between 9/11 exposures and PAD or did not find a positive association between 9/11 exposures and PAD; therefore, they were not eligible for further review. Specific reasons why each of these 26 studies did not provide a medical basis are summarized below.

Of the 26 studies that did not provide sufficient medical basis in **Petition 048a** for PAD, five were supportive of the biological plausibility for a causal relationship between post-traumatic stress disorder (PTSD) and CVD but did not examine 9/11 exposures [Beristianos et al. 2016; Edmondson and von Kanel 2017; Scherrer et al. 2020; O'Donnell et al. 2021; Hargrave et al. 2022].

Two of the 26 studies were cross-sectional studies that evaluated the association between PM exposure and elevated serum lipids, potentially mediating air pollution-related effects on CVD, but did not assess PAD [Shanley et al. 2016; McGuinn et al. 2019].

One of the 26 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 26 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 but did not assess PAD [Ward-Caviness 2019].

Three of the 26 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,[15] and black carbon [Devlin et al. 2014; Ghio et al. 2018; Jhun et al. 2019].

One of the 26 studies examined the association between air pollution exposure and coronary artery calcium scores, which are used to assess coronary atherosclerosis, but did not assess PAD [Kaufman et al. 2016].

Ten of the 26 studies assessed certain CVD outcomes, but not PAD, in 9/11 exposed populations [Wanahita et al. 2010; Jordan et al. 2011b; Jordan et al. 2013; Brackbill et al. 2014; Alper et al. 2017; Cohen et al. 2017; Remch et al. 2018; Yu et al. 2018; Sloan et al. 2021; Yu et al. 2021].

Two of the 26 studies assessed composite outcomes that included PAD but did not find a positive association between 9/11 exposures and those outcomes [Jordan et al. 2018; Li et al. 2023]. For a detailed discussion of these two studies *see* Section VIII.B.2.c., and f.

Finally, one of the 26 studies summarized the discussions and conclusions from an expert workshop pertaining to cardiopulmonary health impacts of $PM_{2.5}$ air pollution on high-risk populations [Newman et al. 2020]. This study described increased CVD risks associated with air pollution exposure, including $PM_{2.5}$, but did not assess PAD.

V. EVALUATED HEALTH CONDITION

In accordance with the *Policy and Procedures* [NIOSH 2026a], the Science Team reviewed the information provided by the petitioner, including medical basis information, and determined that the health condition of interest for this evaluation is PAD, which refers to atherosclerotic disease of the lower extremity [Gerhard-Herman et al. 2017]. It is a chronic, progressive condition caused by atherosclerosis that results in partial or complete blockage of peripheral arteries. PAD most commonly refers to the arteries of the lower limbs, and less frequently affects the upper extremities [Campia et al. 2019].

In PAD of the lower limbs, arterial stenoses arising from atheromatous plaques result in a gradual reduction of blood flow to the limbs. This reduced blood flow eventually manifests clinically as pain and tissue damage; however, many patients with PAD are asymptomatic. The earliest symptom is pain after walking at a certain speed and for a certain amount of time, known as intermittent claudication [Mascarenhas et al. 2014]. PAD is associated with significant morbidity, mortality, and quality of life impairment [Gornik et al. 2024].

Aortic aneurysm is classified under the broad umbrella of PAD in American College of Cardiology Foundation (ACCF) and AHA guidelines, although it is pathologically distinct from the occlusive/stenotic forms of PAD [Olin et al. 2010]. Aortic aneurysms, both

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

abdominal and thoracic, appear to be distinct from atherosclerosis, although some aortic aneurysms may be associated with an atherosclerotic origin [Isselbacher et al. 2022]. For example, most thoracic aortic aneurysms are degenerative and occur in association with risk factors for atherosclerosis such as smoking, hypertension, and hypercholesterolemia [Isselbacher et al. 2022]. However, it remains unclear what role atherosclerosis plays in aortic aneurysm formation.

PAD is the third most common clinical manifestation of atherosclerosis, after ischemic heart disease (IHD) and stroke [Song et al. 2019]. Excluded from the evaluated condition are atherosclerotic aortic disease [Isselbacher et al. 2022] and non-atherosclerotic causes of lower extremity arterial disease, such as vasculitis, fibromuscular dysplasia, physiological entrapment syndromes (e.g., popliteal artery entrapment syndrome), and cystic adventitial disease [Gerhard-Herman et al. 2017].

VI. RISK FACTORS FOR EVALUATED HEALTH CONDITION

A. General Risk Factors

The risk factors for PAD are similar to those found for other types of atherosclerotic disease, e.g., IHD and stroke. PAD risk factors can be classified into those that are modifiable and those that are non-modifiable. Among non-modifiable risk factors, age is a strong determinant of PAD, with risk increasing with advancing age [Song et al. 2019]. In high-income countries like the United States, PAD prevalence is not significantly different between men and women. In contrast, in low- and middle-income countries, women have a higher PAD prevalence compared to men [Song et al. 2019]. Another important non-modifiable risk factor for PAD is Black race [Selvin and Erlinger 2004].

As for modifiable risk factors, PAD is associated with all major atherosclerotic risk factors such as hypertension, obesity, diabetes, hypercholesterolemia, smoking, inflammatory markers (e.g., C-reactive protein levels), IHD, and stroke [Song et al. 2019]. For example, cigarette smoking is associated with a 2- to 4-fold increased PAD risk [Joosten et al. 2012] and diabetes mellitus is also associated with an approximately 2- to 4-fold increase in risk [Campia et al. 2019]. Some studies have also shown that reduced kidney function is a PAD risk factor [Selvin and Erlinger 2004].

B. 9/11 Risk Factors

Compared to the Science Team's previous evaluations for IHD and stroke, fewer research findings are available to identify 9/11 risk factors for PAD. However, among the 9/11 agents listed in the *Inventory* [NIOSH 2018], there is evidence for PM exposure, including $PM_{2.5}$ and PM_{10}, and some metals (i.e., lead and cadmium) being associated with increased PAD risk.

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 micrograms per cubic meter (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].

Serra et al. [2021] provides evidence to suggest that PM_{10} exposure is associated with increased PAD risk. This paper provided crude correlations between PAD prevalence in various countries with pollutant concentrations in those same countries. Few details were provided on how the pollutant concentrations were summarized and analyzed. Pearson's correlation coefficients (R_2 index)[16] were calculated to determine the correlation between various pollutants and PAD prevalence. The authors found that the R_2 index between PM10 exposure and PAD prevalence was 0.5, which the authors interpreted as representing a minimum dependence. In contrast, the R_2 index between PAD prevalence and both $PM_{2.5}$ exposure and benzopyrene was only 0.2.

Several other studies support an association between $PM_{2.5}$ exposure and PAD [Dominici et al. 2006; Peng et al. 2008; Haley et al. 2009; Bell et al. 2014; Talbott et al. 2014].

Bell et al. [2014] used Medicare data from 1999 through 2010 to examine hospitalizations whose principal discharge diagnosis involved PAD, defined as International Classification of Diseases (ICD)-9 440–448, which includes arterial aneurysm and PAD, among those ≥ 65 years. For the PAD outcome, the study included data from 140 counties. Daily county-level $PM_{2.5}$ values were estimated using population-based monitors in each county. Effect estimates for single-day lags of the same day (lag 0), previous day (lag 1), and two days previous (lag 2) were modeled separately. For lag 0, $PM_{2.5}$ exposures that occurred on the same day as the hospital admission were considered. For lag 1, $PM_{2.5}$ exposures that occurred on the day before hospital admission were considered. Finally, for lag 2, $PM_{2.5}$ exposures that occurred two days before hospital admission were considered. $PM_{2.5}$ values at lag 0 were associated with a significantly increased risk of PAD hospital admissions for both sexes combined (percent increase in risk of PAD hospital admissions associated with 10 µg/m^3 increase in $PM_{2.5}$ = 1.26%; 95% confidence interval [CI], 0.48, 2.05) and for males and females separately. At lag 1 and lag 2, findings were similar but were not statistically significant. Earlier but similar studies were conducted by Dominici et al. [2006] and Peng et al. [2008]. Dominici et al. [2006] included Medicare data from 1999 through 2002 and found non-statistically significant increases in risk of PAD hospital admissions associated with a 10 µg/m^3 increase in $PM_{2.5}$. Peng et al. [2008] used Medicare data from 1999 through 2005 and found significantly increased risks of PAD hospital admissions associated with a 10 µg/m^3 increase in $PM_{2.5}$ exposures.

16 If the R_2 index = 1, this represents a strong dependence between the variables and indicates a direct correlation between them; in contrast, a value of 0 means no dependency/correlation. Another way to interpret correlation is to square it (r^2), which gives the proportion of variance in one variable explained by the other. The r^2 of 0.5 is 0.25 or about 25% of the variance is explained by the relationship. In contrast, the r^2 of 0.2 is 0.04 or about 4% of the variance is explained by the relationship.

Talbott et al. [2014] assessed the short-term effects of daily $PM_{2.5}$ air pollution levels on hospitalizations for various CVD outcomes, including PAD, for seven states within the CDC Environmental Public Health Tracking (EPHT) network (Florida, Massachusetts, New Hampshire, New Jersey, New Mexico, New York, and Washington), using a case-crossover design.[17] Predicted daily $PM_{2.5}$ data were linked to the zip code of patient residence. PAD was defined as a principal discharge diagnosis coded as ICD-9 440–449, which includes arterial aneurysm and PAD. The authors included only non-elective (emergency and urgent) in-patient hospitalizations. New Jersey and New York experienced the highest mean $PM_{2.5}$ levels during the studied period (2001–2008) and were the only states that found increased PAD hospitalization associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$, adjusted for temperature and ozone. In both states, the association was observed at lag 0 and for the average from lag 0 through lag 2. The effects were significant only in the winter months. The authors hypothesized that this result may be attributable to differences in the constituents of $PM_{2.5}$ in the winter months compared to the summer months, and the effect of co-morbidities (e.g., viral infection) in the winter months.

Haley et al. [2009] conducted a similar study as Talbott et al. [2014] using EPHT data and a case-crossover design. However, Haley et al. [2009] studied persons discharged only from New York State hospitals, and only between 2001 through 2005 with a primary diagnosis of PAD (ICD-9 440–448). They found a significantly increased risk of PAD hospitalization at lag 0 per 10 $\mu g/m^3$ $PM_{2.5}$. Lags of 1 to 4 days were also examined, but no significant differences were observed using those $PM_{2.5}$ exposure lags.

Not all studies have found an association between $PM_{2.5}$ exposure and PAD. For example, Hoffman et al. [2009] examined the ankle-brachial index (ABI) in a random sample of German residents. Estimated daily mean values for $PM_{2.5}$ at the participant's residence were obtained. The authors did not find an association between ABI and $PM_{2.5}$ exposure. However, they did find an association between PAD (defined as an ABI < 0.9) and residential proximity (≤ 50 meters) to major roads. The authors speculated that exposure to ultrafine particles (which are not 9/11 agents) may explain the association between PAD and residential proximity to major roads.

Lead and cadmium, which are metals and 9/11 agents, are recognized by AHA to be associated with PAD [Lamas et al. 2023]. AHA based their conclusion on several studies. One was a cross-sectional study using 1999–2000 data from the National Health and Nutrition Examination Survey (NHANES) (Navas-Acien et al. 2004). This study found a monotonically and statistically significant increasing risk for PAD (defined as ABI < 0.9) associated with increasing blood levels of both lead and cadmium, even when controlling for smoking. Similar findings were observed for urine cadmium levels in a prospective cohort study of adult American Indian populations conducted between 1989 and 1999 in Arizona, Oklahoma, and the Dakotas [Tellez-Plaza et al. 2013]. Tellez-Plaza et al. [2013] found that those in the highest tertile of urine cadmium levels had a significantly

17 In a case-crossover design, each case serves as its own control. With this design, many important personal characteristics that could be confounders, such as socioeconomic factors and smoking, are controlled for by design. The authors used 28-day strata, and for each case compared exposures at referent times 7, 14, and 21 days before or after the case hospital admission, within the same stratum. The authors made the comparison on the same day of the week to control for personal activity patterns. This design sampled three referent days for every case. *See* Talbott et al. [2014].

increased risk for PAD (defined as ABI < 0.9); however, the PAD risk among those in the middle tertile was non-significantly elevated and the test for trend was also non-significant. A longitudinal cohort study of Swedish women with no femoral plaque at baseline (*n* = 312) found that baseline blood cadmium levels in the highest tertile were significantly associated with increased PAD risk (defined as ABI ≤ 0.9) at follow-up, which occurred approximately 5 years after baseline, after adjustment for smoking and other CVD risk factors [Fagerberg et al. 2013]. That study also found that baseline urine cadmium levels in the highest tertile were non-significantly associated with increased PAD risk at follow-up.

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;[18] (2) review identified studies to determine which studies are high-quality studies for further evaluation;[19] (3) evaluate and integrate the evidence of a causal association between 9/11 exposures and the health condition being evaluated;[20] 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.[21] The Science Team then advises the Administrator of its findings.[22]

VIII. REVIEW OF THE LITERATURE

A. Literature Search

The literature search identifies high-quality published, peer-reviewed epidemiologic studies that provide evidence on the proposed causal association between 9/11 exposure and PAD. 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[23] 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

18 *See Policy and Procedures*, Section III.B. [NIOSH 2026a].
19 *See Policy and Procedures*, Section III.C. [NIOSH 2026a].
20 *See Policy and Procedures*, Section IV. [NIOSH 2026a].
21 *See Policy and Procedures*, Section V. [NIOSH 2026a].
22 *See Policy and Procedures*, Section VI. [NIOSH 2026a].
23 The list of search terms provided coverage for both cardiovascular and cerebrovascular outcomes, although this evaluation was restricted to PAD. Literature providing evidence on IHD and stroke were used in separate evaluations.

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, including the petitions for IHD, stroke, and PAD. 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 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 searches, 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 July 2026. This two-pronged approach ensures all relevant and up-to-date literature is available for the evaluation.

The literature search identified nine peer-reviewed, published, epidemiologic studies of PAD in 9/11-exposed populations for full review as potential studies for evaluation [Jordan et al. 2011a; Mani et al. 2013; Stein et al. 2016; Jordan et al. 2018; Cohen et al. 2019; Colbeth et al. 2020; Li et al. 2023; Singh et al. 2023; Parvin et al. 2026].

One study 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.a. for completeness.

Eight other 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; Jordan et al. 2018; Cohen et al. 2019; Colbeth et al. 2020; Li et al. 2023; Singh et al. 2023; Parvin et al. 2026]. All eight studies were removed from further consideration but are discussed in Section VIII.B.2. for completeness.

B. Studies Removed from Further Consideration

1. Previously Reviewed Studies Removed from Further Consideration

One previously reviewed study that was identified in the literature search was determined by the Science Team not to demonstrate sufficient validity indicators and was removed from further consideration [Mani et al. 2013]. The findings from this study and its notable limitations were discussed in the published decision on **Petition 012**.[24] It is also summarized below for completeness.

a. 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 non-FDNY responders. The bilateral carotid arteries of all subjects were imaged with both multi-contrast MRI and DCE-MRI.[25] For DCE-MRI, the area under the curve (AUC) was calculated at 2 and 7 minutes after contrast agent injection. ABI measures (left and right) were also obtained.[26]

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

24 *See supra*, note 1.

25 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].

26 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 $\leq$ 0.90. ABI is separately measured on the right and left sides of the body. *See* Aboyans et al. [2012].

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 higher 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. The authors did not report if any participants had borderline low or abnormal ABI findings.

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 time 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. Because of these limitations, Mani et al. [2013] was not classified by the Science Team as a high-quality study for this evaluation.

2. Newly Identified Studies Removed from Further Consideration

Eight studies newly 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; Jordan et al. 2018; Cohen et al. 2019; Colbeth et al. 2020; Li et al. 2023; Singh et al. 2023; Parvin et al. 2026].

Six of these eight studies assessed mortality and were excluded for several reasons. First, they conducted external comparisons that were particularly vulnerable to strong selection bias given large differences between the 9/11-exposed population and the general population [Jordan et al. 2011a; Stein et al. 2016; Jordan et al. 2018; Colbeth et al. 2020; Li et al. 2023; Singh et al. 2023]. The external reference population varied by study and was the general population of New York City (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 five studies [Stein et al. 2016; Jordan et al. 2018; Colbeth et al. 2020; Li et al. 2023; Singh et al. 2023].[27] Selection bias would tend to cause underestimation of PAD risks. Second, cause of death information from death certificates by linkages to the CDC National Death Index (NDI)[28] and NYC vital records likely led to death undercounting. Third, the health condition examined by five of these studies [Jordan et al. 2011a; Stein et al. 2016; Jordan et al. 2018; Li et al. 2023; Singh et al. 2023] was not PAD and instead was NIOSH Life Table Analysis System (LTAS)[29] Major 17 (other diseases of the circulatory system). This is a composite outcome that included cerebrovascular diseases (CeVD); hypertension without heart disease; and diseases of the arteries, veins, and lymphatic vessels, including pulmonary embolism, pulmonary hypertension, aortic aneurysm, peripheral arterial disease, thrombophlebitis, and esophageal varices [Robinson et al. 2006; Schubauer-Berigan et al. 2011]. The sixth mortality study, [Colbeth et al. 2020], used a narrower outcome, i.e., NIOSH LTAS Minor 62 (diseases of the arteries, veins, lymph nodes). However, it is also a composite outcome and included pulmonary embolism, pulmonary hypertension, aortic aneurysm, peripheral arterial 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. Finally, none of these six studies reported internal analyses examining the exposure-response association among cohort members for PAD mortality and none of the studies provided any evidence of an association between 9/11-exposures and the composite outcome variable.

The seventh study identified in the literature search, Cohen et al. [2019], was removed from further consideration because it also used a composite outcome. The outcome was the presence of any of the following diagnoses in the FDNY electronic medical record: MI; stroke; unstable angina; coronary artery surgery or angioplasty; CVD death; transient ischemic attack; stable angina; cardiomyopathy; and other CVD (aortic aneurysm, peripheral arterial vascular intervention, and carotid artery surgery).

The eighth study identified in the literature search, Parvin et al. [2026], was removed from further consideration because it did not examine the association between 9/11-exposures and PAD. Instead, it compared the mortality experience of responders enrolled in the WTC Health Program compared to responders who were not enrolled (i.e., WTC Health Registry [WTCHR] enrollees). Parvin et al. [2026] found lower mortality among WTC Health Program-enrolled responders. Each of these eight excluded studies is briefly described below.

a. Jordan et al. [2011a]

Jordan et al. [2011a] examined mortality in a cohort study of WTCHR

27 Note that the Jordan et al. [2018] and Li et al. [2023] mortality studies used two different external reference populations.

28 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/.

29 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 and Kelly-Reif [2022].

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's 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 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 health condition of interest for this evaluation 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 PAD, including body mass index (BMI) and alcohol use. 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 General Responder Cohort (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) being one of the outcomes that was studied. 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. Jordan et al. [2018]

Jordan et al. [2018] expanded and extended follow-up of a previous longitudinal mortality study by 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 the 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 described for Jordan et al. [2011a].

d. Cohen et al. [2019]

In a prospective cohort study, Cohen et al. [2019] examined total CVD incidence that was ascertained for physician-documented diagnoses in the FDNY electronic medical record. The outcome was a composite of various types of CVD, which included: MI; stroke; unstable angina; coronary artery surgery or angioplasty; CVD death; transient ischemic attack; stable angina; cardiomyopathy; and other CVD (aortic aneurysm, peripheral arterial vascular intervention, and carotid artery surgery). 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 609 CVD events during the observation period (147,680 person-years), of which only 2.4% (*n* = 15) were "other CVD." The number of firefighters with PAD was not specified but appear to have been lumped with "other CVD." The authors reported modest, but statistically significant estimates of an association between the composite CVD outcome and different measures of 9/11 exposure

related to time of arrival and length of response. For example, there was a 31% increase in CVD risk in firefighters present at the WTC site for 6 or more months vs. those who worked less time at the site (HR = 1.31; 95% CI: 1.09, 1.58).

A strength of the study is that CVD outcomes were obtained from medical records rather than self-reported information. A key limitation of this study is the lack of PAD-specific analyses. Although PAD events were included within the composite CVD outcome, they accounted for a very low proportion of the total. In addition, the elevated long-term CVD risk observed in these firefighters may reflect the demanding and stressful nature of their occupation, which involves repeated smoke and dust exposures during later fire responses.

e. Colbeth et al. [2020]

The study by Colbeth et al. [2020] is a longitudinal study 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 CDC NDI and grouped deaths by the NIOSH LTAS 119-cause map [Robinson et al. 2006; Schubauer-Berigan et al. 2011]. Among the outcomes explored was NIOSH LTAS Minor 62 (diseases of the arteries, veins, lymph nodes), which is a composite outcome that includes pulmonary embolism, pulmonary hypertension, aortic aneurysm, peripheral arterial disease, thrombophlebitis, and esophageal varices. SMRs and associated 95% CIs 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 Minor 62.

Participants were largely male (96.8%), firefighters (86.0%), non-Hispanic White (87.2%), and never-smokers (60.9%). There were nine deaths observed over the follow-up period (2001–2017) that involved Minor 62. The mortality rate among FDNY responders for Minor 62 was significantly decreased when compared with the general U.S. population (SMR = 0.33; 95% CI: 0.15, 0.63). 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, healthy worker effect, and better access to healthcare. Other limitations include those previously described and inherent to composite outcomes, mortality studies, and external comparisons.

f. 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 after 2010, or who died or reached their 85th birthday during the first year after enrollment 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 [Robinson et al. 2006; Schubauer-Berigan et al. 2011].

The cohort was predominantly male (84.2%), non Hispanic White (71.3%), and never-smokers (59.5%). 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.

g. 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 among WTC-exposed firefighters. 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 analysis was limited to all-cause mortality and did not include PAD or Major 17-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 U.S. 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 death from Major 17 among FDNY firefighters compared with the general U.S. 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.

h. 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 9/11 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 those who were incapacitated and required a proxy to respond to the WTCHR questionnaires. Among the 9,467 FDNY/GRC members in the subset, 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 cardiovascular diseases, based on self-reported diagnosis by a healthcare professional. PAD was not reported to be a comorbidity for which data were collected. 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); (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 and 40 to 49 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). Smoking-related mortality 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 reduced 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.

C. Identified High-Quality Studies

None of the nine peer-reviewed, published, epidemiologic studies of 9/11-exposed populations examining PAD identified in the literature searches were found to have sufficient validity indicators to be considered high-quality studies eligible for further review.[30]

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

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

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[31] and to assign findings regarding causal association to one of five categories[32] as described below in Section IX.A.4. This evaluation includes a consideration of 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 (PAD) is observed; (4) **temporality** of the cause and effect, that is 9/11 exposure precedes the health condition (PAD); (5) **biological gradient** or dose-response relationship where changes in 9/11 exposures are associated with corresponding changes in the magnitude of the outcome (PAD); (6) **biological plausibility** — the extent to which 9/11 studies align with known facts about the biology of the health condition being evaluated (PAD); (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 PAD.

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, or from a limited review of the literature to assess biological

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

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 interrelated nature of several Bradford Hill criteria, including strength of association, consistency of associations, temporality, and biological gradient, as well as considerations of study limitations and representativeness, these aspects may be evaluated collectively when synthesizing evidence from the totality of high-quality studies.

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 one of 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. Summary of Evaluation and Evidence Synthesis

The peer-reviewed, published, epidemiologic studies examining PAD risk in the 9/11-exposed population identified in the literature search were determined to lack sufficient validity indicators to be considered high-quality studies. As a result, there was no evidence available to further evaluate or synthesize.

X. CONCLUSION

The literature search conducted by the Science Team did not identify any high-quality peer-reviewed, published, epidemiologic studies of PAD in 9/11-exposed populations. Therefore, pursuant to the WTC Health Program's *Policy and Procedures* [NIOSH 2026a], there was no evidence available for synthesis by the Science Team. The Science Team concludes that the available scientific evidence for a causal association between 9/11 exposure and PAD is inadequate to determine the likelihood of a causal association (Category V).[33]

33 *See Policy and Procedures*, Section V.E. [NIOSH 2026a].

XI. REFERENCES

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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. Information Provided by the Petitioner and Medical Basis Determination.

Petition Number	Information Provided by Each Petition	Medical Basis[1] (Yes/No)
Petition 048a	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. 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
	5. 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. Inj Epidemiol *4*(1):17, https://doi.org/10.1186/s40621-017-0115-x	No
	6. 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, https://doi.org/10.1001/jamanetworkopen.2019.9775	Yes
	7. 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	No
	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://pmc.ncbi.nlm.nih.gov/articles/PMC12703491/	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

Petition Number	Information Provided by Each Petition	Medical Basis[1] (Yes/No)
Petition 048a (cont.)	10. Newby DE, Mannucci PM, Tell GS, et al. [2015]. Expert position paper on air pollution and cardiovascular disease. Eur Heart J *36*(2):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, 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	No
	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
	16. Lioy PJ, Weisel CP, Millette JR, et al. [2002]. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC 11 September 2001. Environ Health Perspect *110*(7):703–714, https://pmc.ncbi.nlm.nih.gov/articles/PMC1240917/	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	No
	18. McGuinn L, Schneider A, McGarrah R, et al. [2019]. Association of long-term $PM_{2.5}$ 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

Petition Number	Information Provided by Each Petition	Medical Basis[1] (Yes/No)
Petition 048a (cont.)	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 RB, Smith CB, 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
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	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	No
	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. 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
	27. 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
	28. 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	Yes

Petition Number	Information Provided by Each Petition	Medical Basis[1] (Yes/No)
Petition 048a (cont.)	29. 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
	30. 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
	31. 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
	32. 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
	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

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 published, peer-reviewed 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.

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