Form Approved
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Exp. Date 12/31/2021

Petition for the Addition of a New WTC-Related Health Condition for Coverage under the World Trade Center (WTC) Health Program

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

General Instructions

Any interested party may petition the WTC Program Administrator to add a condition to the List of WTC-Related Health Conditions (List) in 42 C.F.R. Part 88 (see http://www.cdc.gov/wtc/faq.html#hlthcond for the complete list).

Please use this form to petition the Administrator to add a health condition (any recognized medical condition requiring treatment or medication) to the List. Please use a separate form for each health condition.

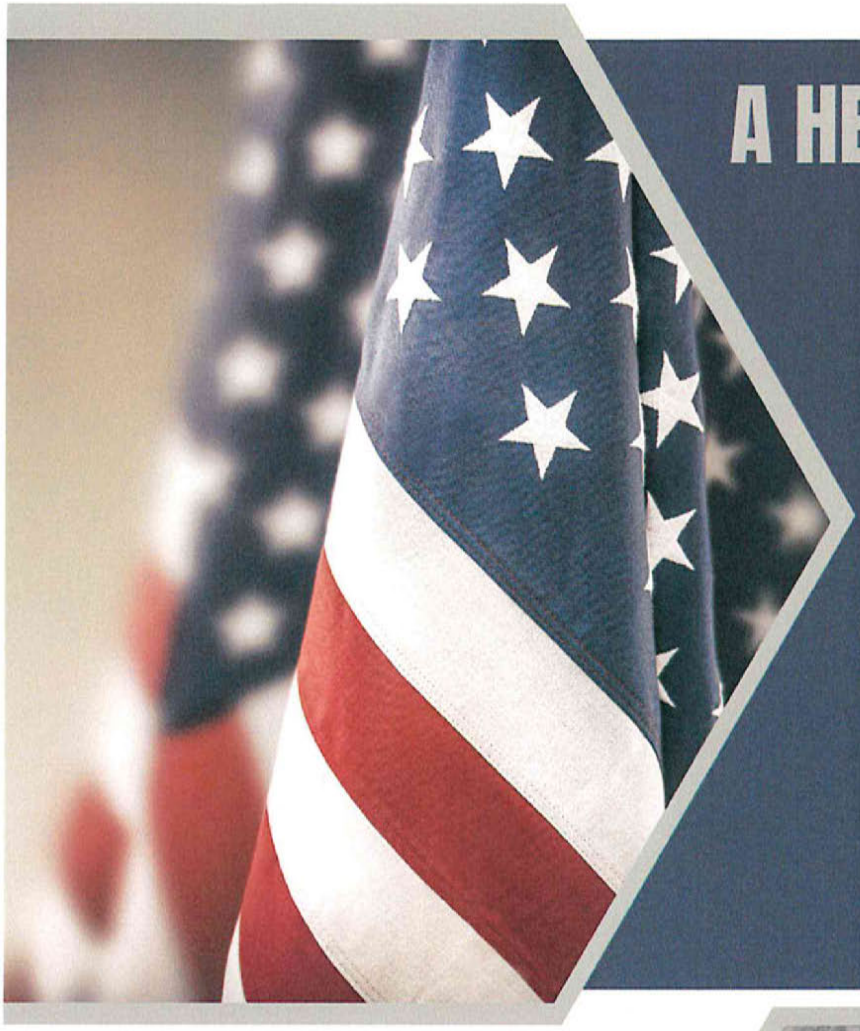
Use of this petition *form* is voluntary, but any petition must include all of the information identified below, as required by 42 C.F.R. Part 88. Petitions that do not provide the required information will not be considered by the WTC Program Administrator. Additional supporting materials may be submitted and are encouraged.

Please note, however, the petition and all supporting materials submitted to the WTC Health Program are part of the public record and may be subject to public disclosure. Personal information will be redacted prior to public disclosure.

Please TYPE or PRINT all information clearly on the form.

If you need more space to provide the required information, please attach additional pages to this form.

Mail or email this form to: World Trade Center Health Program
395 E. Street, S.W., Suite 9200
Washington, D.C. 20201
WTC@cdc.gov



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A. Interested Party Information

A1. Do you represent an organization (are you submitting this petition on behalf of an organization)?
☑ Yes (Go to A2) ☐ No (Go to A3)

A2. Organization Information:

Pulse 4 Pulse LLC
Name of organization

A3. Name of Individual Petitioner or Organization Representative:

[redacted]
First name Last name

[redacted]
Position, if representative of organization

A4. Mailing Address:

[redacted]
Street

[redacted]
City State Zip code

A5. Telephone Number: [redacted]

A6. Email Address: [redacted]

B. Proposed WTC-Related Health Condition Information

B1. Health Condition Information:

Cardiovascular Disease
Name of health condition you wish to petition to add to the List of covered conditions

If the name of the condition is not known, please provide a description of the condition or the name of the diagnosis provided by a physician or other healthcare provider.

C. Basis for Proposing that the Condition Be Added to the List of WTC-Related Health Conditions

C1. Describe the reasons the WTC Program Administrator should consider the addition of this health condition. Explain how the health condition you are proposing relates to the exposures that may have occurred from the September 11, 2001, terrorist attacks. Your explanation must include a medical basis for the relationship/association between the 9/11 exposure and the proposed health condition. The medical basis may be demonstrated by reference to a peer-reviewed, published, epidemiologic study about the health condition among 9/11 exposed populations or to clinical case reports of health conditions in WTC responders or survivors. First-hand accounts or anecdotal evidence may not be sufficient to establish medical basis. If you need more space, please attach additional pages to this form.

(Attached document)

D. Signature of Petitioner

Sign your name below to indicate that you are petitioning the WTC Program Administrator to consider adding a health condition to the list of WTC-related health conditions identified in 42 C.F.R. Part 88.

[redacted] [redacted]

Signature Date

Privacy Act Statement

In accordance with the Privacy Act of 1974, as amended (5 U.S.C. § 552a), you are hereby notified of the following:

Title I of the James Zadroga 9/11 Health and Compensation Act of 2010 amended the Public Health Service Act (PHS Act) to establish the World Trade Center (WTC) Health Program. Sections 3311, 3312, and 3321 of Title XXXIII of the PHS Act require that the WTC Program Administrator develop regulations to implement portions of the WTC Health Program established within the Department of Health and Human Services (HHS). The WTC Health Program is administered by the Director of the National Institute for Occupational Safety and Health (NIOSH), within the Centers for Disease Control and Prevention (CDC). The information provided with this form and supporting documentation will be used by the WTC Program Administrator to consider the disposition of a petitioned-for health condition. Disclosure of this information is voluntary.

Records containing information in identifiable form become part of an existing NIOSH system of records under the Privacy Act, 09-20-0147, "Occupational Health Epidemiological Studies and EEOICPA Program Records and WTC Health Program Records, HHS/CDC/NIOSH." These records are treated in a confidential manner, unless otherwise compelled by law.

Information submitted to WTC Health Program which may be considered "protected health information" pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Pub. L. 104–191; 42 U.S.C. § 1320d) and the HIPAA Privacy, Security, Breach Notification, and Enforcement Rules (45 C.F.R. pts. 160, 162, and 164) will be maintained in accordance with all applicable laws.

NIOSH may disclose information in identifiable form only insofar as such disclosure is permitted pursuant to the HIPAA Privacy Rule; this may include disclosure to the WTC Health Program Scientific/Technical Advisory Committee (STAC), which may be asked to consider the petition and issue a recommendation to the WTC Program Administrator. Information in identifiable form will be redacted from submitted petition forms and supporting documentation that become a part of the public record (e.g. in conjunction with STAC consideration or a rulemaking).

Proposal for the Addition of Cardiovascular Disease as a New World Trade Center-Related Health Condition for Coverage under the World Trade Center (WTC) Health Program.

The effects of exposure to the WTC following the terrorist attacks have been varied and necessitated the need for continued studies and evaluations to better understand the scope of health conditions and diseases that have resulted from this incident and subsequent exposure to the resulting fumes and toxins.

With time and continued monitoring, it has become evident that First Responders, especially those most exposed to the dust and toxins are increasingly developing cardiovascular disease (CVD). Initial studies to assess the risk of cardiovascular disease were mixed. However, more recently there are studies that show quite conclusively that exposure to WTC disaster does increase the risk of cardiovascular disease in the long term.

In a study done by Hillel W. Cohen et al (1), 9,796 male firefighters in the FDNY were evaluated. For each participant, the association between WTC exposure and risk of CVD was assessed between September 9, 2001 and December 31, 2017. CVD risk was assessed in association with two measures of WTC exposure: arrival time to the WTC and duration of work at the WTC. Data analyses were conducted from May 1, 2018 to March 8, 2019.

Findings showed that both acute WTC exposure as well as repeated exposure for at least 6 months at the WTC site appeared to be associated with long term elevated CVD risk. Consequently, the continued need for long term monitoring of the health of the survivors is suggested.

In another study, Nancy L Sloan et al (2) assessed WTC - related exposure to toxic materials associated with annual and cumulative CVD incidence and risk over 17 years in the World Trade Center Health Program (WTCHP) General Responder Cohort (GRC).

After 9/11, 37,725 responders were evaluated regarding the first occurrence of CVD which constituted coronary artery disease, myocardial infarction, stroke and/or congestive heart failure. Information was obtained from physician reported diagnosis or current treatment of any of the listed conditions reported in WTCHP GRC monitoring visits.

The incidence of CVD and the CVD hazard ratio associated with 9/11/ 2001 were calculated using statistical analyses. It showed to date, 6.3% reported new CVD overall. The CVD arrival risks were higher for those with dust exposure compared to those without dust exposure and were higher in women compared to men.

The study concluded that WTCHP GRC members with 9/11/2001 exposures had substantially higher CVD risk than those who began working at the WTC after 9/11, this is consistent with observations among WTC-exposed New York City firefighters. Women's risk was greater than that of men's. GRC-elevated CVD risk may also be occurring at a younger age than in the general population.

In a third study, Molly Remch et al (3), performed an observational prospective cohort study of 6481 blue-collar first responders who are part of the World Trade Center Health Program (WTCHP) in New York City. They sought to determine whether post-traumatic stress disorder

(PTSD) is a risk factor for myocardial infarction (MI) and stroke beyond the expected effects from recognized cardiovascular risk factors and depression. Baseline measures were recorded in 2012 and 2013. Participants were followed for 4 years.
Results showed that the prevalence of PTSD was 19.9% in men and 25.9% in women, that is, at least twice that of the general population. Cumulative incidence of MI or stroke was consistently larger for men or women with PTSD across follow-up. In men free of depression, WTC dust exposure had no effect. The study concluded that PTSD is a risk factor for MI and stroke to the same extent in men as in women, independent of depression.

For the above listed reasons, we would like to petition the WTC Program Administrator to consider the addition of Cardiovascular Diseases including Coronary Artery Disease, Myocardial Infarction, Stroke and Congestive Heart Failure as WTC-Related Health Conditions.

Pulse4Pulse LLC can assist in promoting the health of the members of WTCHP in a cost effective manner. Through a non-invasive 15 to 20 minute diagnostic test, asymptomatic members with evidence of microvascular and large artery disease can be identified. Microvascular disease with large artery stiffness and decreased compliance is seen in early stages of uncontrolled hypertension and other risk factors of cardiovascular diseases. If left untreated it can progress to advanced cardiovascular disease which is much more complicated and expensive to treat (4), (5).
Getting ahead of catastrophic cardiovascular disease can provide significant cost savings to WTCHP

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RESEARCH ARTICLE

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Cardiovascular disease in the World Trade Center Health Program General Responder Cohort

Nancy L. Sloan DrPH[1] | Moshe Z. Shapiro MS[1] | Ahmad Sabra MS, MPH[1] | Christopher R. Dasaro MA[1] | Michael A. Crane MD[2] | Denise J. Harrison MD[3] | Benjamin J. Luft MD[4] | Jacqueline M. Moline MD[5] | Iris G. Udasin MD[6] | Andrew C. Todd PhD[1] | Susan L. Teitelbaum PhD[1]

[1]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[2]Department of Environmental Medicine and Public Health, World Trade Center Health Program Clinical Center of Excellence, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[3]School of Medicine, World Trade Center Health Program Clinical Center of Excellence, NYU Langone Medical Center, New York University, New York, New York, USA

[4]Department of Medicine, World Trade Center Health Program Clinical Center of Excellence, Stony Brook University Medical Center, Stony Brook, New York, USA

[5]Department of Occupational Medicine, Epidemiology and Prevention, World Trade Center Health Program Clinical Center of Excellence, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA

[6]World Trade Center Health Program Clinical Center of Excellence, Environmental and Occupational Health Sciences Institute, Rutgers University Biomedical Sciences, Piscataway, New Jersey, USA

Correspondence

Nancy L. Sloan, DrPH, Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, Box 1057, New York 10029, USA.
Email: nancy.sloan@mssm.edu

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Abstract

Background: Over 90,000 rescue and recovery responders to the September 2001 World Trade Center (WTC) attacks were exposed to toxic materials that can impair cardiac function and increase cardiovascular disease (CVD) risk. We examined WTC-related exposures association with annual and cumulative CVD incidence and risk over 17 years in the WTC Health Program (HP) General Responder Cohort (GRC).

Methods: Post 9/11 first occurrence of CVD was assessed in 37,725 responders from self-reported physician diagnosis of, or current treatment for, coronary artery disease, myocardial infarction, stroke and/or congestive heart failure from WTCHP GRC monitoring visits. Kaplan–Meier estimates of CVD incidence used the generalized Wilcoxon test statistic to account for censored data. Cox proportional hazards regression analyses estimated the CVD hazard ratio associated with 9/11/2001 arrival in responders with and without dust cloud exposure, compared with arrival on or after 9/12/2001. Additional analyses adjusted for comorbidities.

Results: To date, 6.3% reported new CVD. In covariate-adjusted analyses, men's CVD 9/11/2001 arrival risks were 1.40 (95% confidence interval [CI] = 1.26, 1.56) and 1.43 (95% CI = 1.29, 1.58) and women's were 2.16 (95% CI = 1.49, 3.11) and 1.59 (95% CI = 1.11, 2.27) with and without dust cloud exposure, respectively. Protective service employment on 9/11 had higher CVD risk.

Conclusions: WTCHP GRC members with 9/11/2001 exposures had substantially higher CVD risk than those initiating work afterward, consistent with observations among WTC-exposed New York City firefighters. Women's risk was greater than that of men's. GRC-elevated CVD risk may also be occurring at a younger age than in the general population.

KEYWORDS

cardiovascular disease, environmental exposure, occupation, responder/recovery worker, World Trade Center

1 | INTRODUCTION

Heart disease continues to be the leading cause of death worldwide,[1–3] only recently surpassed by cancer among middle-aged people in the United States and other high-income countries.[4] Major risk factors include older age, cigarette smoking, diet and obesity, high blood pressure, high cholesterol, diabetes, and work psychosocial stressors.[1-3,5-7] In some studies,[8-14] exposure to air pollution, radioactive materials, some environmental toxic metals, and other particulate matter have been associated with cardiac function damage and increased risk of heart disease and death. Others have found null or negative associations of such exposures with cardiovascular risk and disease, and this lack of association is sometimes attributed to a healthy worker effect.[15-18]

In response to the 9/11/2001 terrorist attacks on the World Trade Center (WTC), more than 90,000 people participated in rescue and recovery efforts and in debris cleanup.[19,20] These responders were exposed to a complex mix of toxins, including burning jet fuel from the hijacked airplanes and hazardous particulate matter from the collapse of the WTC towers.[21,22] In addition to physiologic stress, many responders experienced work psychosocial stressors that can initiate or exacerbate unhealthy chronic biologic processes and behavioral responses and influence CVD risk.[7,23] These exposures have been associated with increased short-term and persistent risk of morbidity, including respiratory disease, gastro–esophageal reflux disorder, posttraumatic stress disorder (PTSD), and certain cancers.[20,24-26]

An analysis of WTC Registry responders and non-responders through 2009 who had high levels of exposure were found to have death rates from heart disease that were more than twice the rates observed in those with less exposure to the environmental site contaminants.[27] By 2014, female WTC Registry members who had intense dust cloud exposure had a 1.28 times higher risk of physician-diagnosed heart disease than less exposed women (95% confidence interval [CI] = 1.02, 1.61), whereas men with intense dust cloud exposure had a 1.14 (95% CI = 0.97, 1.34) times higher rate of physician-diagnosed heart disease than men with less exposure.[28] In an early 4-year responder follow-up, higher risks for PTSD-mediated heart attack and stroke were observed in surviving responders involved in debris cleanup.[29] For the earliest arriving firefighter responders, who were exposed to the toxic dust cloud on 9/11/2001, a 1.44 (95% CI = 1.09, 1.90) higher risk of primary cardiovascular disease (CVD) was observed compared with responders who had less toxic exposure arriving on or after 9/12/2001.[30]

Using 17 years of follow-up of the WTC Health Program's (HP) large, diverse General Responder Cohort (GRC) of both men and women, this study's objective was to examine the annual and cumulative incidence of CVD. We also investigated the association of CVD risks with 9/11/2001 exposures, based on whether or not the responders reported being exposed to the dust cloud, compared with those arriving on or after 9/12/2001.

2 | MATERIALS AND METHODS

This study was conducted in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance.

2.1 | Study population

The WTCHP GRC is an open (continuing to enroll) cohort. Through March 31, 2019, 32,539 men and 5186 women general responders who reported whether they had or had not been diagnosed with or treated for CVD have been followed.

2.2 | WTCHP GRC eligibility criteria and recruitment

The WTCHP GRC recruited its participants using publicity and broad outreach through various mechanisms (volunteers, community and labor organizations; governmental and legislative agencies and media). Men and women eligible for the WTCHP GRC include those who worked or volunteered at the tower sites in lower Manhattan, at the Staten Island landfill or on certain barge-loading piers for at least 4 h between September 11 and 14, 2001, who worked at least 24 h between September 11 and 30, 2001 or at least 80 h between September 11 and July 31, 2002. The WTCHP GRC comprises rescue and recovery workers and volunteers who were enrolled in the HP on or after July 16, 2002.[31] This includes staff who had contact with WTC-related human remains from the Office of the Chief Medical Examiner between September 11, 2001 and July 31, 2002, and those from the Port Authority Trans-Hudson Corporation who cleaned tunnels for at least 24 h between February 1, 2002 and July 1, 2002.[32] Other responders who may not be included in the WTCHP GRC are employees of the Fire Department of the City of New York (FDNY), individuals participating in the New York City Department of Health Registry (~23% also participate in the WTCHP GRC), Pentagon and Shanksville responders, Nationwide Provider Network members (not WTCHP GRC participants), and others participating and not participating in similar programs.[20,28]

2.3 | Data collection

Responders voluntarily participating in the program were first interviewed (beginning July 2002) to assess their sociodemographic characteristics and WTC-related exposures, after which they received a comprehensive, standardized physical and mental health examination. Program participants were subsequently interviewed and examined every 12–18 months, depending upon their presentation for program visits. The data were collected, using a standardized clinical interview, from each WTCHP GRC participant at each monitoring visit from July 16, 2002.

Data available at the time of analysis, through March 31, 2019, were analyzed.

2.4 | Data source

CVD was defined as a responder's self-report of a physician's first diagnosis or responders' reporting that they were under current treatment for first-time coronary artery disease (CAD), myocardial infarction (MI), stroke, or congestive heart failure (CHF). Only monitoring visit reports of diagnosis or treatment on or after 9/11/2001 are classified as having post 9/11 CVD. Responders were classified as not having post 9/11 CVD if they did not report a physician diagnosis or treatment for any of these conditions. Additionally, reported heart murmur and other heart diseases were not included in the definition of CVD. Individuals solely reporting heart murmur or other heart diseases were retained as noncases in the analysis.

Exposure was categorized by self-report as follows: first arrival at the WTC site on 9/11/2001 reporting exposure to the dust cloud (very high exposure); first arrival on 9/11/2001 not reporting exposure to the dust cloud (high exposure); and first arrival on or after 9/12/2001 (low/intermediate exposure).

2.5 | Statistical analyses

We conducted analyses to compare the effects of more intense (very high and high) with less intense (low/intermediate) WTCHP GRC exposures. The conditional cumulative incidence of post 9/11 first-time CVD was assessed by Kaplan–Meier analyses, using the generalized Wilcoxon test statistic to account for censored data. Responders with pre-existing (before 9/11/2001) CVD were excluded from this evaluation to ensure any association with WTC exposure was not attributable to prior CVD history ($n = 302$). Age-to-diagnosis, which simultaneously adjusts for time since 9/11 and age at 9/11, was estimated as the age at the reported earliest post 9/11 date of a physician's diagnosis of CAD, MI, stroke, or CHF and 9/11/2001.[33] As the analysis includes a maximum of 17 years' follow-up, results were censored at the most recent follow-up fewer than 17 years before March 31, 2019. The annual incidence was calculated as each year's difference in cumulative incidence. Cox proportional hazards regression analyses were conducted to estimate the risk of CVD associated with high and very high exposure compared with low/intermediate exposure. As men constitute the large majority of WTCHP GRC and their results were almost identical to the total sample results, adjusted Cox proportional hazards regression analyses were conducted stratified by responders' sex. To determine the influence of potential confounders, covariate-adjusted analyses included race/ethnicity. Additional Cox proportional hazards models included comorbidities and risk factors that could have been influenced by their WTC exposure and are in the causal pathway for CVD. These variables include self-reported lifetime cigarette smoking, cholesterol, hypertension, and diabetes status, and measured initial visit body mass index (BMI). Cigarette smoking was classified as never (the referent value), former, or current smoker. Height and weight were measured at each visit. Initial visit BMI was calculated as 703 × measured weight in pounds/(measured height in inches)^2 and then categorized as <25 (normal), 25 to <30 (overweight), ≥30 (obese). At each monitoring visit, responders reported whether they had ever been diagnosed with high cholesterol, hypertension, and diabetes. Associations with these comorbidities, (not having high cholesterol, hypertension, or diabetes, respectively, are the referent groups), were examined in the comorbidity-adjusted analyses as risk factors in the causal pathway of WTC exposure and CVD. Because the responders' reported dates were frequently missing for the first physician diagnosis of high cholesterol, high blood pressure, and/or diabetes; their categories are reported as "ever or never diagnosed" and do not reflect cases solely diagnosed before the first CVD date of diagnosis.

Being employed in high-stress occupations has been associated as a CVD risk factor.[34,35] As over half of the WTCHP GRC were engaged in the high-stress occupation of protective services on 9/11, sensitivity analyses were conducted to evaluate whether protective services occupation on 9/11/2001 influenced the observed results. Cross-tabulations were conducted to determine whether the proportion of those actively engaged in protective services varied by WTC 9/11 arrival time with and without self-reported exposure to the dust cloud, and dichotomous variables were added to the Cox regressions to assess their associations with CVD risk and how 9/11 protective services occupation influenced the effects of WTC 9/11 exposures. Further analyses were conducted by including, in the statistical models, diagnosis of cancer since 9/11/2001, and unknown cancer status before CVD as proxies for having potentially received cancer treatment that may have increased the risk of CVD.[36] To assess recall bias, we also examined whether the age of reported CVD diagnosis was influenced by when the WTCHP GRC participants enrolled in the health monitoring program.

All variables calculated using dates imputed missing days as each month's midpoint, missing month as June, and missing year only when information from a consecutive visit could clarify the missing year. Missing covariate values were recoded to the sex-specific mode value in the multivariate analyses, which was the referent value of zero except for high cholesterol, BMI, and occupation on 9/11. For consistency with the other comorbidities (and because nearly 50% of men and women reported ever being diagnosed or treated for high cholesterol), missing data for high cholesterol was set to the referent value of zero for both sexes. Missing BMI was set to obese for men and overweight for women. For the sensitivity analyses for protective services, missing occupation was conservatively coded as the referent value of 'not protective services.'

The Cox proportional hazards assumption was assessed via Schoenfeld residuals. No violations were found for the primary factors of interest except in the comorbidity-adjusted sensitivity analyses for protective services. Sensitivity analysis adding log survival time interactions for the violating covariates and comorbidities was

used to address the variables where proportionality was violated. Analyses included all WTCHP GRC who provided written voluntary consent for research data aggregation and who presented for at least one monitoring visit. In addition to the previously mentioned exclusions, responders with unknown arrival date on the WTC site or unknown dust cloud exposure ($n = 1005$); and responders with unknown sex ($n = 1$) or age ($n = 1$) were also excluded from the analysis.

Descriptive statistics were conducted using SPSS 24.0 (IBM Corp.). The Cox proportional hazards analyses and Schoenfeld tests of the proportional hazards models were conducted in Stata (StataCorp. 2019, Stata Statistical Software: Release 16; StataCorp LLC.).

3 | RESULTS

This analysis includes 37,725 WTCHP GRC, 86% male (Table 1). Most were between 30 and 59 years old with a median age of 37 (ranging from 19 to 80) years old on 9/11/2001. Most of the responders were married, white non-Hispanic, never smoked cigarettes, and employed in protective services on 9/11/2001. Half the participants enrolled in the WTCHP GRC before 2008, another 25% enrolled between 2008 and 2013, and 25% enrolled after 2013. Those enrolled before 2008 have participated in 6 ± 4 health monitoring visits (range, 1–14), and those enrolled between 2008 and 2013 have participated in 5 ± 3 (range, 1–11) visits. Those enrolled in 2014 and after have participated in 2 ± 2 health monitoring visits. Twenty-one percent have made only one health monitoring visit, 53% of whom enrolled in 2014 or after, 32% of whom enrolled before 2008, and 14% of whom enrolled between 2008 and 2013. Nineteen percent first arrived at the WTC site on 9/11/2001 and reported being exposed to the toxic dust cloud (men: 19.5%, women: 16.2%); 25.6% arrived on 9/11/2001 and reported that they were not exposed to the dust cloud (men: 26.2%; women: 22.3%); and 55.3% (men: 54.3%; women: 61.5%) arrived on or after 9/12/2001.

To date, 6.3% ($n = 2385$) of WTCHP GRC reported having been diagnosed with or treated for first-time CVD (Table 2). More than half of the reported CVD cases are CAD (3.8%), followed by stroke (1.8%), MI (1.3%), and CHF (0.7%). While male and female responders' prevalence of post 9/11 stroke and CHF are similar, men's prevalence of CAD and MI are nearly three times that of women. The mean age at CVD diagnosis was 52.4 ± 9.0 years, with an average of 7.9 ± 4.7 years since 9/11/2001 when diagnosed. The age and years since 9/11/2001 at diagnosis did not vary by sex; there was also little variation in age at diagnosis across CVD conditions.

Some CVD comorbidity was observed. A considerable percentage diagnosed with CAD also reported heart attacks (15.3%), stroke (5.1%), and CHF (2.8%; Figure 1); few ($n = 36$, 1.5%) had reported three or more CVD conditions.

Within 5 years of 9/11/2001, the annual CVD incidence increased from <1% in all responders by 0.7% in the general responders who initiated work on or after 9/12, compared with 1.2% among those presenting for work on 9/11/2001 (Table 3, Figures 2 and 3). Eight years after 9/11/2001, the mean time for the cohort's

TABLE 1 WTCHP GRC participant characteristics ($n = 37,725$)

	N	%
Age (years) on 9/11/2001		
20–29	1153	3.1
30–39	8871	23.5
40–49	15,021	39.8
50–59	9188	24.4
60+	3492	9.3
Sex		
Male	32,539	86.3
Female	5186	13.7
Race/ethnicity		
White	20,241	53.7
Black	3422	9.1
Asian	464	1.2
Hispanic	6992	18.5
Other, not reported	6606	17.5
Cigarette smoker		
Never	21,754	57.7
Former	9713	25.7
Current	2651	7.0
Missing	3607	9.6
Occupation on 9/11/2001		
Protective services/military	19,968	52.9
Construction	6601	17.5
Electrical, telecom, and other installation and repair	2463	6.5
Transportation and material moving occupations	2008	5.3
Other jobs	4744	12.6
Unemployed/retired	516	1.4
Not reported	1425	3.8
Marital status on 9/11/2001 ($n = 37,434$)		
Single	4184	11.1
Married or partnered	27,084	71.8
Separated or divorced	5539	14.7
Widowed	627	1.7
Missing	291	0.8
Initial body mass index (703 × pounds/inches^2)		
<25 (normal)	5263	14.3
25 to <30 (overweight)	15,373	41.8
≥30	16,146	42.8
Missing	943	2.5
Ever diagnosed with diabetes	5193	13.8
Missing	125	3.3
Ever diagnosed with high cholesterol	19,672	52.1
Missing	4099	10.9
Ever diagnosed with high blood pressure	16,167	42.9
Missing	155	0.4
WTCHP GRC exposure based on arrival at site		
On or after 9/12	20,866	55.3
On 9/11, not dust cloud	9673	25.6
On 9/11, in dust cloud	7186	19.0

TABLE 1 (Continued)

	N	%
Year of WTCHP GRC enrollment		
≤2007	18,874	50.0
2008–2013	9231	24.5
≥2014	9620	25.5

Abbreviations: GRC, General Responder Cohort; WTCHP, World Trade Center Health Program.

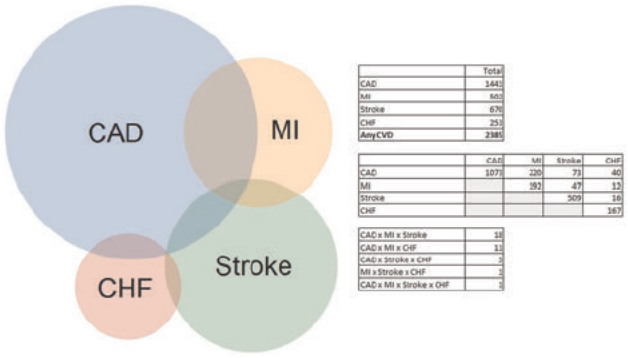

FIGURE 1 Distribution of post 9/11 CVD ($n = 2385$) in World Trade Center Health Program General Responder Cohort. CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; MI, myocardial infarction

CVD diagnoses, the annual incidence in those arriving on or after 9/12/2001 had quadrupled to 2.0% compared with 2.5% and 3.1%, among those arriving on 9/11/2001 who were not and who were exposed to the dust cloud, respectively. The cumulative incidence across these exposure groups remained similar until the fourth year after 9/11/2001. By eight years after 9/11/2001, the cumulative CVD incidence was 12.5% among those arriving on 9/11/2001 not exposed to the dust cloud and 13.5% among those exposed to the dust cloud, compared with 9.6% in those arriving on or after 9/12. The CVD incidence patterns were virtually identical among men and women (data not shown).

Men's covariate-adjusted risk of CVD was substantially higher in 9/11/2001 arrivals not exposed to the dust cloud ($HR_{cov} = 1.43$; 95% CI = 1.29, 1.58) and in those exposed to the dust cloud ($HR_{cov} = 1.40$; 95% CI = 1.26, 1.56) than that of general responders arriving on or after 9/12/2001 (Table 4). Additional adjustment for comorbidities reduced men's overall risk compared with those arriving later to $HR_{cov\_comorb} = 1.33$; 95% CI = 1.20, 1.47 in those without dust cloud exposure and hazard ratio (HR) = 1.29; 95% CI = 1.16, 1.44 in those with dust cloud exposure. There was no substantial violation of the proportional hazards assumptions in the covariate-adjusted model; however, some violation of the assumptions was observed for smoking, cholesterol, and BMI status in the model adjusted for comorbidities. The sensitivity analysis adding log survival time interactions for the violating variables (BMI, smoking, and cholesterol status) produced nearly identical risk estimates as the non-timed dependent model ($HR_{cov\_comorb} = 1.33$; 95% CI = 1.20, 1.47 in those without dust cloud exposure and $HR_{cov\_comorb} = 1.28$; 95% CI = 1.15, 1.43 in those with dust cloud exposure).

Women's covariate-adjusted risks were $HR_{cov\_comorb} = 1.59$; 95% CI = 1.11, 2.27 in responders arriving on 9/11/2001 without dust cloud exposure and $HR_{cov\_comorb} = 2.16$; 95% CI = 1.39, 3.11 in responders arriving on 9/11/2001 with dust cloud exposure, compared with women arriving on or after 9/12. When adjusted for comorbidities, women arriving on 9/11/2001 without dust cloud exposure had $HR_{cov\_comorb} = 1.49$; 95% CI = 1.04, 2.13 and $HR_{cov\_comorb} = 2.17$; 95% CI = 1.34, 3.14 with dust cloud exposure compared with women arriving on or after 9/12/2001. No violation of the proportional hazards assumptions was observed in the women's analyses.

Except for Hispanic men who had lower CVD risk than white non-Hispanic responders in the covariate-adjusted model, the hazards ratios for race/ethnicity all had 95% CIs that included the null value of 1. Current cigarette smokers had higher CVD risk in men and women, but former smokers only had higher CVD risk in women than lifetime nonsmokers. Overweight and obesity at a responder's first visit was associated with CVD risk but only significantly so in men.

TABLE 2 CVD (CAD, MI, stroke, CHF) prevalence in WTCHP GRC[a]

	Diagnosed on/after 9/11								
	Men ($n = 32,539$)			Women ($n = 5186$)			Total ($n = 37,725$)		
	N	%	Age at diagnosis; mean (SD)	N	%	Age at diagnosis; mean (SD)	N	%	Age at diagnosis; mean (SD)
Coronary artery disease	1360	4.2	53.2 (8.6)	81	1.6	53.1 (9.9)	1441	3.8	53.2 (8.7)
Heart attack (MI)	476	1.1	52.3 (7.6)	26	0.5	54.4 (10.2)	502	1.3	52.4 (7.8)
Stroke	586	1.8	52.8 (9.6)	84	1.6	51.2 (10.6)	670	1.8	52.6 (9.7)
Congestive heart failure	226	0.7	51.3 (10.1)	27	0.5	49.5 (10.6)	253	0.7	51.2 (10.2)
Total reporting ≥1 CVD	2192	6.7	52.5 (8.8)	193	3.7	51.8 (10.4)	2385	6.3	52.4 (9.0)

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; GRC, General Responder Cohort; MI, myocardial infarction; WTCHP, World Trade Center Health Program.

[a]Conditions not mutually exclusive.

TABLE 3 Kaplan–Meier cumulative and annual cardiovascular disease incidence by years since 9/11/2001 ($n = 37,725$)

Years since 9/11/2001																		
Cumulative incidence (%)																		
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
≥9/12	0.4	0.9	1.6	2.7	3.5	4.7	5.9	7.6	9.6	11.5	13.7	15.8	18.5	22.1	25.6	30.4	36.4	43.1
9/11, not in dust	0.3	0.7	1.7	3.0	4.5	6.1	8.0	10.0	12.5	14.2	16.7	19.4	22.8	28.7	34.6	43.3	49.7	NA
9/11, in dust cloud	0.4	0.9	1.7	2.9	4.7	6.4	8.3	10.4	13.5	15.8	18.6	22.3	25.9	27.9	33.7	40.7	45.8	55.2
Annual incidence (%)																		
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
≥9/12		0.5	0.7	1.1	0.8	1.2	1.2	1.7	2.0	1.9	2.2	2.1	2.7	3.6	3.5	4.8	6.0	6.7
9/11, not in dust		0.4	1.0	1.3	1.5	1.6	1.9	2.0	2.5	1.7	2.5	2.7	3.4	5.9	5.9	8.7	6.4	NA
9/11, in dust cloud		0.5	0.8	1.2	1.8	1.7	1.9	2.1	3.1	2.3	2.8	3.7	3.6	2.0	5.8	7.0	5.1	9.4
Number at risk																		
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
≥9/12	20,865	15,032	8676	7300	6392	5954	5463	4924	4360	3825	3287	2846	2381	1823	1347	994	640	56
9/11, not in dust	9672	6725	3622	2974	2584	2373	2127	1904	1666	1441	1257	1071	883	645	480	316	159	15
9/11, in dust cloud	7185	5124	2860	2309	2004	1834	1642	1457	1289	1100	955	793	661	477	362	263	161	28

Responders who had ever been diagnosed with diabetes, high blood pressure, and/or high cholesterol had significantly higher CVD risk than those never diagnosed with those conditions, except in women with high blood pressure. The associations with smoking, cholesterol, and BMI status should not be over-interpreted as violations of the proportional hazards assumptions were observed for these indices. In additional multivariate analyses (data not shown), having been diagnosed with cancer before CVD was highly associated with CVD.

WTCHP GRC protective services occupational status on 9/11/2001 was significantly different among those arriving on or after 9/12/2001 than those responding on 9/11/2001. Over 65% of men and 71% of women 9/11 arrivals (in those exposed and not exposed to the dust cloud) were engaged in protective services employment on 9/11. Only 42% of men and 44% of women arriving on or after 9/12 were engaged in protective services on 9/11. Therefore, sensitivity analyses adjusting for protective services occupation on 9/11 were conducted. Compared with all other responders, active occupation in protective services on 9/11/2001 was associated with increased risk of CVD in men ($HR_{cov} = 2.07$; 95% CI = 1.89, 2.27) and women ($HR_{cov} = 2.81$; 95% CI = 2.02, 3.90; Table 5). Higher protective services HRs were observed in the comorbidity-adjusted models. Adjustment for 9/11/2001 protective services occupational status reduced the CVD risks associated with 9/11/2001 arrival, particularly in the comorbidity-adjusted analysis of men reporting dust cloud exposure and in both the covariate and covariate/comorbidity-adjusted analysis of women not reporting dust cloud exposure, to risks with confidence limits crossing the null value of 1. Sensitivity

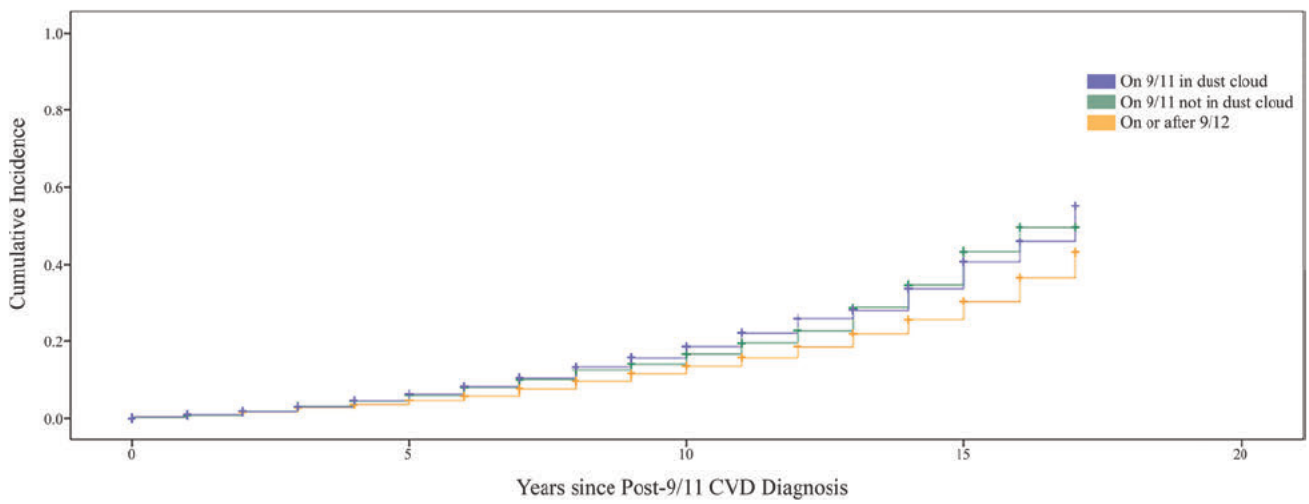

FIGURE 2 Kaplan–Meier post 9/11 cardiovascular disease (CVD) incidence by years since 9/11/2001

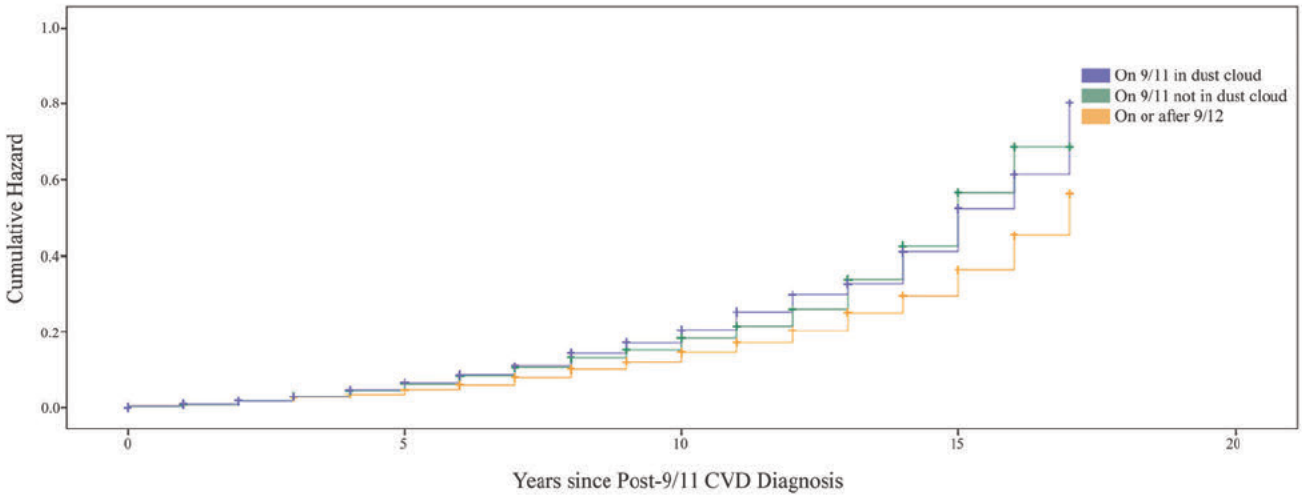

FIGURE 3 Kaplan–Meier post 9/11 cardiovascular disease (CVD) cumulative hazard by years since 9/11/2001

analyses adding log survival time interactions for the violating covariates and comorbidities produced similar results. Analyses of the total sample (both sexes) combining arrivals on 9/11 with and without dust cloud exposure that were adjusted for 9/11 protective services occupation had a 9/11 arrival $HR_{cov} = 1.21$; 95% CI = 1.12, 1.32 in the covariate-adjusted model and $HR_{cov\_comorb} = 1.12$; 95% CI = 1.03, 1.22 (with no violations for the primary factor of interest).

Because those enrolling later in the health monitoring program had fewer visits, we assessed whether age at diagnosis varied by enrollment period. Men who enrolled in the first 5 years of the monitoring program (50% of men's CVD cases) reported they were 53 ± 9 years old at their first CVD diagnosis, as did the men who enrolled in the last 4 years of the program (26% of men's CVD cases). Men who enrolled between 2008 and 2013 reported being a year and a half younger (±9 years) at their first CVD diagnosis. Women who enrolled in the first 5 years (before 2007, 58% of women's cases) and the following 5 years (2008–2013, 25% of women's cases) reported being 51 ± 10 years old at their first CVD diagnosis, whereas the 17% ($n = 33$) enrolled in the last 4 years reported they were 56 ± 13 years old at their first diagnosis of CVD.

4 | DISCUSSION

Globally, heart disease remains the leading cause of death.[1-3] In some studies, exposure to air pollution, radioactive materials, environmental toxic metals, and other particulate matter identified in the WTC disaster have been associated with increased risk of cardiac dysfunction, heart disease, and death. With 17 years' follow-up of a large cohort of WTC general responders, we observed substantially higher risks of CVD associated with initiating work on 9/11/2001 compared with responders who initiated work on or after 9/12.

This study found 9/11/2001 arrival was associated with elevated CVD risk in men and women compared with responders arriving on or after 9/12. Despite the somewhat different definitions of CVD used in our and in the FDNY analyses, the analysis of men's risk adjusted for nearly identical covariates and comorbidities demonstrate WTC 9/11 exposures are associated with large, statistically significant increased hazards for CVD, consistent with observations in the all-male sample of firefighter responders.[30] This consistency with the male FDNY results is notable, as their criteria for CVD was based upon the theoretically more accurate (than a responder's recall, particularly regarding event dates) physicians' diagnosis from electronic medical records.[30] Except for women presenting on 9/11/2001 without dust cloud exposure, the WTCHP GRC lower 95% CIs were all well above 1. The association with dust cloud exposure was less clear among men, who comprise the vast majority of the sample, whereas a clear elevated CVD risk was observed with arrival on 9/11 in the total sample.

Distinct from the FDNY responders, the WTCHP GRC includes a substantial female cohort. With its large sample of female general responders, the WTCHP GRC also identified large risk differences associated with 9/11/2001 compared with later exposure among female responders, even though there was a 45% lower post 9/11/2001 CVD prevalence among female than male responders. The risk in women associated with 9/11/2001 exposure was much greater than the elevated men's 9/11/2001 CVD risk compared with those presenting on or after 9/12/2001. This may indicate that the female general responders have less chronic or previous hazardous environmental exposures and, therefore, have a greater reaction to the toxic 9/11/2001 exposures than do men. Alternatively, because the cohort of female general responders is so much smaller than that of men, they may simply represent a less diverse group of responders than men. Women's hazards ratios had wider 95% CIs than that of men's, reflecting the smaller sample size for female responders.

Over half of the WTCHP GRC were employed in protective services (high-stress occupations) which, among other occupations (such as transportation and moving materials) have been identified as CVD risk factors.[34,35] Employment in protective services was associated with CVD, and specifically attenuated the risks of men with dust cloud exposure risks to the extent that their confidence limits crossed the value of 1 (no effect). Conversely, adjustment for 9/11

TABLE 4 Cox proportional hazards regression of age to CVD diagnosis

	Men (n = 32,539)				Women (n = 5186)			
		95% CI				95% CI		
	HR	Lower	Upper	p	HR	Lower	Upper	p
Covariate adjusted								
9/11, not in dust cloud	1.43	1.29	1.58	≤0.001	1.59	1.11	2.27	0.01
9/11, in dust cloud	1.40	1.26	1.56	≤0.001	2.16	1.49	3.11	≤0.001
White, non-Hispanic								
Black, non-Hispanic	0.79	0.68	0.92	0.003	1.84	1.28	2.64	≤0.001
Asian, non-Hispanic	1.23	0.84	1.81	0.28	0.44	0.06	3.18	0.41
Hispanic	0.83	0.73	0.95	0.006	1.28	0.89	1.82	0.18
Other or not reported	1.03	0.91	1.16	0.66	0.90	0.51	1.58	0.72
Covariate and comorbidity adjusted								
9/11, not in dust cloud	1.33	1.20	1.47	≤0.001	1.49	1.04	2.13	0.03
9/11, in dust cloud	1.29	1.16	1.44	≤0.001	2.17	1.50	3.14	≤0.001
White, non-Hispanic								
Black, non-Hispanic	0.87	0.74	1.01	0.07	1.52	1.04	2.24	0.03
Asian, non-Hispanic	1.13	0.77	1.67	0.53	0.62	0.08	4.54	0.64
Hispanic	0.95	0.83	1.08	0.41	1.31	0.91	1.90	0.15
Other or not reported	1.03	0.91	1.15	0.67	0.95	0.54	1.66	0.85
Nonsmoker								
Former smoker	0.98	0.89	1.07	0.59	1.42	1.03	1.96	0.03
Current smoker	1.55	1.33	1.80	≤0.001	1.89	1.09	3.28	0.02
Normal (BMI < 25)								
Overweight (BMI, 25–29)	1.25	1.07	1.47	0.005	1.04	0.71	1.51	0.86
Obese (BMI ≥ 30)	1.56	1.34	1.83	≤0.001	1.31	0.89	1.92	0.17
Ever had diabetes	1.21	1.10	1.33	≤0.001	1.52	1.07	2.16	0.02
Ever had high blood pressure	1.46	1.31	1.63	≤0.001	1.28	0.92	1.78	0.14
Ever had high cholesterol	5.61	4.92	6.39	≤0.001	2.76	1.93	3.94	≤0.001

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

occupation in protective services obviated the excess CVD risk in women without dust cloud exposure. These observations suggest that the risks associated with protective services employment share common characteristics with 9/11 arrival, although there was no significant interaction between arrival time and 9/11 protective services occupation (data not shown). Still, when all 9/11 arrivals for the total sample (both sexes, whether exposed to the dust cloud or not) were combined, adjustment for being engaged in protective services on 9/11 reduced but did not nullify the excess CVD risk in the WTCHP GRC.

Known risk factors for CVD include age, poor diet, cigarette smoking, high blood pressure, high cholesterol, diabetes, and work psychosocial stressors.[2,3,5-7,23,34,35] Analyses adjusted and stratified for these risk factors were conducted. Consistent with the literature,[1-3] being Hispanic was associated with lower men's CVD risk in the covariate-adjusted analyses, but not in the remaining analyses where the confidence limits for race/ethnicity risk crossed the null value of 1. The associations of measured BMI at the first health monitoring visit and smoking were generally in the expected direction. Although the observed associations with the participants' reports of ever being diagnosed with high blood pressure, high cholesterol, and diabetes were in the expected direction, they are flawed in this evaluation because dates of their initial diagnoses were often missing, offering no assurance that these conditions occurred before the self-reported CVD diagnosis. As violations of the proportional hazards assumptions were observed for smoking, cholesterol, and BMI status, their associations with CVD risk in this study should not be over-interpreted. Adjustment for comorbidities and risk factors, including smoking, overweight and obesity, hypertension, diabetes, and high cholesterol, all of which may be partially caused or exacerbated by the 9/11/2001 exposures, and are in the causal pathway for CVD, may overcontrol and underestimate the 9/11 exposure effects.

The WTCHP GRC CVD risk may also be occurring much earlier than observed in the general population. The WTCHP GRC's average age at heart attack was 52 years old compared with the US general population with an average age at heart attack of 64 in men and

TABLE 5 Cox proportional hazards regression of age to CVD diagnosis including protective services occupation on 9/11/2001

	Men (n = 32,539)				Women (n = 5186)			
		95% CI				95% CI		
	HR	Lower	Upper	p	HR	Lower	Upper	p
Covariate adjusted								
9/11, not in dust cloud	1.24	1.12	1.38	≤0.001	1.25	0.87	1.80	0.23
9/11, in dust cloud	1.14	1.02	1.28	0.02	1.71	1.17	2.48	0.005
White, non-Hispanic								
Black, non-Hispanic	0.83	0.71	0.97	0.02	1.49	1.03	2.16	0.04
Asian, non-Hispanic	1.31	0.89	1.91	0.17	0.34	0.05	2.47	0.29
Hispanic	0.86	0.75	0.98	0.02	1.25	0.88	1.78	0.21
Other or not reported	1.04	0.92	1.17	0.53	0.81	0.46	1.42	0.47
Protective services	2.07	1.89	2.27	≤0.001	2.81	2.02	3.90	≤0.001
Covariate and comorbidity adjusted								
9/11, not in dust cloud	1.16	1.05	1.28	0.005	1.18	0.82	1.70	0.38
9/11, in dust cloud	1.04	0.93	1.17	0.46	1.61	1.10	2.36	0.02
White, non-Hispanic								
Black, non-Hispanic	0.91	0.78	1.06	0.22	1.20	0.81	1.78	0.37
Asian, non-Hispanic	1.16	0.79	1.71	0.44	0.42	0.06	3.14	0.40
Hispanic	0.97	0.85	1.11	0.66	1.28	0.89	1.85	0.19
Other or not reported	1.00	0.89	1.13	0.97	0.83	0.47	1.47	0.53
Nonsmoker								
Former smoker	1.02	0.93	1.12	0.62	1.33	0.97	1.84	0.08
Current smoker	1.77	1.52	2.06	≤0.001	1.67	0.96	2.91	0.07
Normal (BMI < 25)								
Overweight (BMI, 25–29)	1.20	1.02	1.41	0.03	0.96	0.66	1.41	0.84
Obese (BMI ≥ 30)	1.46	1.25	1.71	≤0.001	1.19	0.81	1.75	0.38
Ever had diabetes	1.25	1.14	1.38	≤0.001	1.44	1.01	2.06	0.04
Ever had high blood pressure	1.48	1.33	1.65	≤0.001	1.33	0.96	1.85	0.09
Ever had high cholesterol	5.50	4.83	6.27	≤0.001	2.90	2.03	4.15	≤0.001
Protective services	2.16	1.97	2.37	≤0.001	2.94	2.10	4.11	≤0.001

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

70 in women.[2,3,5,6,37] In the WTCHP GRC, only 4% of CVD occurred at or after age 65. Among the WTCHP GRC, 16% of men's heart attacks occurred before age 45 compared with 4%–10% of men's heart attacks in the general population.[38]

This investigation used robust statistical methods to assess the association of WTCHP GRC environmental exposure and CVD risk among a large cohort of men and women. Categorizing those with a reported heart murmur and other heart diseases as noncases may have attenuated the observed results. Similarly, if responders, particularly those engaged in physically demanding work, are relatively healthy and thus at lower risk for adverse health outcomes, this healthy worker effect may have biased our observed effects of 9/11 exposure toward the null. The results also depend upon the accuracy of participant reports of diagnosis and/or treatment for CVD, in this study. The CVD conditions assessed in this study are major life events. Regardless, the validity of self-reported CVD is imperfect. Correct case identification of MI has been found to be better (ranging from 50% to 98%) than stoke (ranging from 38% to 81%) in various populations.[39-41] While overreporting is more common than underreporting, bidirectional misreporting has been observed. The lack of lifetime primary care medical records, against which to validate the health monitoring program's self-reported CVD diagnoses, is a study limitation. The consistency of men's elevated CVD risk with that of the FDNY suggests that the men's self-reported physician's diagnosis of CVD was not unduly influenced by recall bias. Relatively few women reporting CVD enrolled in the last 4 years of the monitoring program, and the influence of any women's recall bias may be limited. The results are consistent with the extant literature in both the direction and magnitude of 9/11/2001 exposure effects and its higher risk of heart disease.[27-30] While the FDNY data were limited to male responders, Jordan et al. also found an increased risk of heart disease in female responders with intense dust cloud exposure compared with less exposed women.[28,30,42]

As a voluntary program, the extent to which WTCHP GRC participants represent all WTC first responders is unknown. Compared with the FDNY program, the WTCHP GRC provides services

to and obtains information on a more diverse group of general responders. While continuing to enroll responders, the WTCHP GRC has experienced diminishing numbers of responders presenting for monitoring visits over time. The considerable decline in and the possible self-selection of responders presenting for HP monitoring visits among those who are symptomatic or ill potentially explains the increasingly high cumulative incidence over time.

In summary, this evaluation observed a substantially higher risk of CVD associated with WTCHP GRC members initiating work on 9/11/2001 compared with those who initiated work on or after 9/12, with women's risk greater than that of men's. Elevated CVD risk may also be occurring at a younger age in responders than in the general population. Active engagement in protective services on 9/11/2001 is associated with increased CVD risk. The study findings reinforce the need for broadening public awareness about the associations of WTC exposure and CVD and for continued monitoring of the WTCHP GRC to identify and treat heart disease and promote CVD prevention (e.g., through diet, exercise, weight control, smoking cessation, work stressor reduction, etc.) as a means to minimize its life-altering and life-threatening consequences.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Paul A. Landsbergis declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

Nancy L. Sloan and Susan L. Teitelbaum conceived and designed the work; Michael A. Crane, Denise J. Harrison, Benjamin J. Luft, Jacqueline M. Moline, and Iris G. Udasin participated in data acquisition, Nancy L. Sloan conducted the analysis, and Nancy L. Sloan, Moshe Z. Shapiro, Ahmad Sabra, Christopher R. Dasaro, and Susan L. Teitelbaum participated in the interpretation of data; all authors participated in drafting or critically revising the work for important intellectual content in its final approval and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The relevant data are available within the manuscript. The access to the study's de-identified data and analytic code requires IRB approval, and submission and approval of the WTC Data Center Data Use Agreement, and Data Request Form (including an attestation), which may be requested of the corresponding author.

ETHICS APPROVAL AND INFORMED CONSENT

This study has been conducted in accordance with the principles of the Declaration of Helsinki 1975, as revised in 2013, and complies with the ethical standards of the relevant national and institutional committees on human experimentation. The work was performed and the WTCHP research has been approved by the Institutional Review Boards (IRBs) of the Icahn School of Medicine at Mount Sinai (formerly Mount Sinai School of Medicine), New York, NY and the program's other clinical sites, including New York University Langone Medical Center, New York University School of Medicine, New York, NY; Department of Medicine, Stony Brook University Medical Center, Stony Brook, NY; Department of Occupational Medicine, Epidemiology and Prevention, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; and Environmental and Occupational Health Sciences Institute, Rutgers University, Piscataway, NJ.

DISCLAIMER

The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the National Institute for Occupational Safety and Health.

ORCID

Nancy L. Sloan https://orcid.org/0000-0002-3381-7602

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Original Investigation | Occupational Health

Long-term Cardiovascular Disease Risk Among Firefighters After the World Trade Center Disaster

Hillel W. Cohen, DrPH, MPH; Rachel Zeig-Owens, DrPH, MPH; Cynthia Joe, MPH; Charles B. Hall, PhD; Mayris P. Webber, DrPH, MPH; Michael D. Weiden, MS, MD; Krystal L. Cleven, MD; Nadia Jaber, RPA-C; Molly Skerker, BA; Jennifer Yip, MPH; Theresa Schwartz, MS; David J. Prezant, MD

Abstract

IMPORTANCE Published studies examining the association between World Trade Center (WTC) exposure on and after September 11, 2001, and longer-term cardiovascular disease (CVD) outcomes have reported mixed findings.

OBJECTIVE To assess whether WTC exposure was associated with elevated CVD risk in Fire Department of the City of New York (FDNY) firefighters.

DESIGN, SETTINGS, AND PARTICIPANTS In this cohort study, the association between WTC exposure and the risk of CVD was assessed between September 11, 2001, and December 31, 2017, in FDNY male firefighters. Multivariable Cox regression analyses were used to estimate CVD risk in association with 2 measures of WTC exposure: arrival time to the WTC site and duration of work at the WTC site. Data analyses were conducted from May 1, 2018, to March 8, 2019.

MAIN OUTCOMES AND MEASURES The primary CVD outcome included myocardial infarction, stroke, unstable angina, coronary artery surgery or angioplasty, or CVD death. The secondary outcome (all CVD) included all primary outcome events or any of the following: transient ischemic attack; stable angina, defined as either use of angina medication or cardiac catheterization without intervention; cardiomyopathy; and other CVD (aortic aneurysm, peripheral arterial vascular intervention, and carotid artery surgery).

RESULTS There were 489 primary outcome events among 9796 male firefighters (mean [SD] age on September 11, 2001, was 40.3 [7.4] years and 7210 individuals [73.6%] were never smokers). Age-adjusted incident rates of CVD were higher for firefighters with greater WTC exposure. The multivariable adjusted hazard ratio (HR) for the primary CVD outcome was 1.44 (95% CI, 1.09-1.90) for the earliest arrival group compared with those who arrived later. Similarly, those who worked at the WTC site for 6 or more months vs those who worked less time at the site were more likely to have a CVD event (HR, 1.30; 95% CI, 1.05-1.60). Well-established CVD risk factors, including hypertension (HR, 1.41; 95% CI, 1.10-1.80), hypercholesterolemia (HR, 1.56; 95% CI, 1.28-1.91), diabetes (HR, 1.99; 95% CI, 1.33-2.98), and smoking (current: HR, 2.13; 95% CI, 1.68-2.70; former: HR, 1.55; 95% CI, 1.23-1.95), were significantly associated with CVD in the multivariable models. Analyses with the all-CVD outcome were similar.

CONCLUSIONS AND RELEVANCE The findings of the study suggest a significant association between greater WTC exposure and long-term CVD risk. The findings appear to reinforce the importance of long-term monitoring of the health of survivors of disasters.

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Key Points

Question Is World Trade Center exposure on and after September 11, 2001, associated with long-term cardiovascular disease risk in Fire Department of the City of New York firefighters?

Findings In this cohort study of 9796 firefighters, age-adjusted incident rates of cardiovascular disease were higher for firefighters with greater World Trade Center exposure. Both acute World Trade Center as well as repeated exposure during 6 or more months at the World Trade Center site appeared to be associated with long-term elevated cardiovascular disease risk.

Meaning These findings suggest the continued need for long-term monitoring of the health of survivors of disasters.

Author affiliations and article information are listed at the end of this article.

Introduction

The collapse of the World Trade Center (WTC) towers on September 11, 2001 (9/11), produced an enormous dust cloud and created a hazardous environment for first responders, workers, and area residents. Thousands of Fire Department of the City of New York (FDNY) firefighters were exposed on 9/11 and for up to 10 months thereafter. Studies of the FDNY cohort have repeatedly shown that WTC exposure was directly associated with the proximate and long-term risk of obstructive airways disease, sinus disease, and other conditions, including posttraumatic stress disorder (PTSD); these associations have persisted for years after 9/11.[1-7]

Cardiovascular disease (CVD) has long been the greatest source of mortality and morbidity in the United States.[8] Decades of research have identified major modifiable risk factors for CVD, including hypertension, high cholesterol levels, insulin resistance, and cigarette smoking.[8] Environmental exposures have more recently emerged as factors of concern.[9,10] Studies associating CVD with environmental particulate matter have relied on residence or employment as markers of long-term exposure to air pollution or traffic exhaust, consistent with a chronic disease model.[11] Other studies have noted an increase in CVD events on the same day as elevated air pollution measurements, suggesting a pulmonary or inflammatory response from an acute exposure.[10,12-15] Similarly, among residents of neighborhoods exposed to WTC dust, CVD-related hospital admissions increased soon after 9/11.[16-18]

Studies examining associations of WTC exposure with longer-term CVD outcomes have reported inconsistent findings. In one study, WTC exposure was found to be associated with an elevated risk of CVD events,[19] while others reported no associations.[20-22] This longitudinal cohort study examined long-term CVD events in a well-defined cohort of FDNY firefighters, established before 9/11, who responded to the WTC disaster and worked at the site over subsequent months. In particular, we assessed whether acute and postacute exposure to the WTC site was associated with elevated long-term CVD risk.

Methods

Study Population

We followed up the cohort of FDNY firefighters who reported first arrival at the WTC site in the 2 weeks after 9/11 and were actively employed on 9/11 (N = 10 637). Owing to small numbers and the likely different CVD risk profile, women (n = 25) were excluded, as were those who did not provide consent (n = 803), had prevalent CVD (n = 12), and lacked follow-up information (n = 1); 9796 firefighters were included in the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study was approved by the Albert Einstein College of Medicine institutional review board. Participants provided written informed consent; they did not receive financial compensation.

Procedures

In 1997, the FDNY Medical Monitoring Program initiated regular health examinations that currently include both active and WTC-exposed retired personnel. Evaluations are scheduled every 12 to 18 months and incorporate self-administered, computer-based questionnaires and physician examinations, as previously described.[2] Program physicians also document diagnoses of conditions that presented during the period between visits.

CVD Outcomes

Consistent with other studies, we used 2 definitions of CVD outcomes.[23,24] The primary outcome was a diagnosis in the FDNY electronic medical record of any of the following: myocardial infarction, stroke, unstable angina, coronary artery surgery or angioplasty, or CVD death. The secondary outcome (all CVD) included primary outcome events or any of the following: transient ischemic

attack; stable angina, defined as either medication prescribed for angina or cardiac catheterization without intervention; cardiomyopathy; and other CVD (aortic aneurysm, peripheral arterial vascular intervention, and carotid artery surgery). If a participant had more than 1 outcome event, primary events took precedence; among events in the same group, we analyzed the one with the earlier diagnosis date. Two of us (M.D.W. and N.J.) reviewed the detailed physician notes recording the diagnosis to confirm the categorization; disagreement was resolved by one of us (K.L.C.). Cardiovascular disease death information was obtained through linkage to the National Death Index. Some, but not all, of the specific dates of the CVD events were known. Therefore, for consistency, the year of the event was used for all events.

WTC Exposure

Two measures of WTC exposure were assessed based on questionnaire responses because work records were not available. As in previous studies, arrival time, which was our measure of acute exposure, was defined as follows[1-5]: participants who reported their first arrival at the site during the morning of 9/11 (arrival group 1) were considered the most exposed because they were present during or immediately after the towers collapsed. Those who arrived that afternoon were categorized as arrival group 2. Arrival group 3 included those who first arrived on 9/12, and participants who arrived between days 3 and 14 were denoted as arrival group 4.[2] Analyses combined arrival groups 3 and 4 as the reference cohort.

The second, postacute exposure measure, was based on the number of months in which participants worked at the WTC site, beginning 9/11 and ending July 24, 2002, when the site was officially closed to the FDNY. Values were assigned representing the number of months in which a participant reported working at the site for 1 or more days.[2,25,26] We dichotomized the duration variable using the top quartile as the cutoff (working ≥6 months vs <6 months as reference).

Additional Study Variables

We combined information from FDNY employee records, medical records, and questionnaires to construct covariates that included baseline values for hypertension, diabetes, hypercholesterolemia, smoking, and PTSD, along with age, race/ethnicity, and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared). Hypertension was defined as a systolic blood pressure of 140 mm Hg or above or a diastolic blood pressure of 90 mm Hg or above, self-reported hypertension medication use, or physician's diagnosis of hypertension. Diabetes was defined as a fasting blood glucose level of 126 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555), self-reported diabetes medication use, or physician's diagnosis of diabetes. Hypercholesterolemia was defined as a total cholesterol level of 200 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0259), or self-reported hypercholesterolemia medication use or physician's diagnosis of high cholesterol level. Cigarette smoking history was categorized as current smoker, former smoker, or never smoker based on self-report. Posttraumatic stress disorder at baseline was defined using 2 measures. Beginning on October 2, 2001, the FDNY-modified PTSD Checklist (PCL-m) was administered.[26] Beginning December 27, 2005, the FDNY used the PTSD Checklist (PCL-17).[27,28] The earliest measurement from either the PCL-m or the PCL-17 was used; 528 participants (approximately 6%) completed the PCL-17 as their first measure. In the PCL-m, 14 questions were modified to fit the context of 9/11; answer choices were binary (yes or no). To score as having PTSD with the PCL-m, we required symptoms within each of the 3 *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* PTSD symptom groups. We found this modified measure to be similar to the PCL-17.[26,29] When the PCL-17 was used, a score of 44 or higher was considered positive for PTSD.[27,28] Since both the PCL-m and PCL-17 are screening rather than diagnostic tools, our PTSD designation indicates probable PTSD. Race/ethnicity was categorized as non-Hispanic white and other. Body mass index was categorized as normal or underweight (category 1; ≤24.9), preobesity (category 2; 25.0-29.9) obesity class I (category 3; 30.0-34.9), obesity class II

(category 4; 35.0-39.9), and obesity class III (;category 5; ≥40.0). For each variable, the first available measure after 9/11 was considered the baseline value.

Statistical Analysis

Baseline characteristics were compared across arrival groups and duration groups using the χ^2 test for categorical variables and analysis of variance for age. Age-adjusted incidence rates per 1000 person-years were calculated for the primary CVD outcome and all CVD and reported by exposure categories.

Adjusted hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards regression models. Because age is a risk factor for CVD, we used age as the time scale in the models. Follow-up began at age on 9/11 and ended at the youngest of age at event (if applicable), age at end of study (December 31, 2017), age at last FDNY health examination, or age at death. Models were first adjusted for race/ethnicity alone, and then for race/ethnicity, BMI, hypertension, hypercholesterolemia, diabetes, smoking, and PTSD. A *P* value for linear trend was assessed to test whether the association between the 3 arrival time groups and CVD was linear. First-order interactions of covariates with the exposure variables were assessed. In addition, we fit models that included both exposure variables in the same model. Schoenfeld residuals were examined to assess violation of the proportional hazards assumptions.[30] Multivariable models were constructed for both the primary outcome and all CVD.

We conducted a sensitivity analysis by substituting the first PCL-17 measurement for the baseline PCL-m measurement and repeated the primary analyses. Accordingly, we began follow-up at the age on January 1, 2006, and used covariate values from the first available measure after January 1, 2006. Participants who were censored before January 1, 2006, in the primary analysis were similarly excluded from this sensitivity analysis.

P values for HRs were derived from Wald statistics; a 2-tailed α level of .05 was used to denote statistical significance. Data analyses were conducted from May 1, 2018, to March 8, 2019, using SAS software, version 9.4 (SAS Institute Inc).

Results

The study population included 9796 male firefighters; most were never smokers (7210 of 9796 [73.6%]) and non-Hispanic white (9225 of 9796 [94.2%]). The **Table** reports the distribution of covariates by each exposure measure: arrival group and duration of work. Arrival time at the site was significantly associated with age (group 1 mean [SD] age: 40.3 [7.2] years; group 2, 40.1 [7.4] years; groups 3 and 4, 40.8 [7.6] years; *P* < .001), race/ethnicity (group 1, non-Hispanic white: 1476 [91.9%]; group 2, 5001 [94.8%]; groups 3 and 4, 2748 (94.3%); *P* < .001), current smoker (group 1, 199 [12.3%]; group 2, 620 [11.8%]; groups 3 and 4, 341 [11.7%]; *P* = 0.02), and probable PTSD (group 1, 322 [20.0%]; group 2, 520 [9.9%]; groups 3 and 4, 173 [5.9%]; *P* < .001). Duration of work between group 1 vs 2 was significantly associated with age (mean [SD] age, 38.9 [6.8] vs 40.8 [7.5] years; *P* < .001), race/ethnicity (non-Hispanic white, 2287 [95.1%] vs 6938 [93.9%]; *P* = .02), and probable PTSD (327 [13.6%] vs 688 [9.3%]; *P* < .001).

In more than 16 years of follow-up, there were 489 primary outcome events. The distribution of events over time for the primary outcome and for all CVD is shown in **Figure 1**. Events included 120 myocardial infarctions, 61 cerebrovascular accidents, 71 coronary artery bypass grafts, 236 percutaneous coronary interventions, and 1 congestive heart failure. There was a total of 6 CVD deaths; each was preceded by a primary CVD outcome, which was considered the first outcome event. All CVD included an additional 120 events, including 12 transient ischemic events, 54 angina, 39 cardiomyopathies, and 15 other CVD. As shown in **Figure 2**, for the primary CVD cohort, the age-adjusted incident rates (IRs) were higher for those who arrived in the morning at the site (IR, 5.56; 95% CI, 4.42-6.69), while those who arrived in the afternoon (IR, 3.31; 95% CI, 2.92-3.71) and those who arrived on following days (IR, 2.40; 95% CI, 1.99-2.81) had lower rates.

Table. Population Characteristics by Arrival Group and Duration Group

Variable	No. (%)							
	Arrival Group[a]				Duration Group[b]			
	Group 1	Group 2	Groups 3 and 4	*P* Value[c]	Group 1	Group 2	*P* Value[c]	Total
Total, men	1607	5274	2915	NA	2404	7392	NA	9796
Age, mean (SD), y[d]	40.3 (7.2)	40.1 (7.4)	40.8 (7.6)	<.001	38.9 (6.8)	40.8 (7.5)	<.001	40.3 (7.4)
BMI[e]								
Category 5	15 (0.9)	38 (0.72)	23 (0.8)	.61	17 (0.7)	59 (0.8)	.39	76 (0.8)
Category 4	71 (4.4)	232 (4.4)	124 (4.3)		107 (4.5)	320 (4.3)		427 (4.4)
Category 3	449 (27.9)	1443 (27.4)	782 (26.8)		662 (27.5)	2012 (27.2)		2674 (27.3)
Category 2	918 (57.1)	3059 (58.0)	1668 (57.2)		1400 (58.2)	4245 (57.4)		5645 (57.6)
Category 1	145 (9.0)	480 (9.1)	308 (10.6)		204 (8.5)	729 (9.9)		933 (9.5)
Missing	9 (0.6)	22 (0.4)	10 (0.3)		14 (0.6)	27 (0.4)		41 (0.4)
Race/ethnicity								
Non-Hispanic white	1476 (91.9)	5001 (94.8)	2748 (94.3)	<.001	2287 (95.1)	6938 (93.9)	.02	9225 (94.2)
Other	131 (8.2)	273 (5.2)	167 (5.7)		117 (4.9)	454 (6.1)		571 (5.8)
Cigarette smoking status								
Current	199 (12.3)	620 (11.8)	341 (11.7)	.02	271 (11.3)	889 (12.0)	.38	1160 (11.8)
Former	221 (13.8)	700 (13.3)	466 (16.0)		327 (13.6)	1060 (14.3)		1387 (14.2)
Never	1178 (73.3)	3933 (74.6)	2099 (72.0)		1792 (74.5)	5418 (73.3)		7210 (73.6)
Missing	9 (0.6)	21 (0.4)	9 (0.3)		14 (0.6)	25 (0.3)		39 (0.4)
Composite hypercholesterolemia[f]								
Yes	889 (55.3)	2962 (56.2)	1680 (57.6)	.26	1347 (56.0)	4184 (56.6)	.64	5531 (56.5)
No	710 (44.2)	2286 (43.3)	1220 (41.9)		1044 (43.4)	3172 (42.9)		4216 (43.0)
Missing	8 (0.5)	26 (0.5)	15 (0.5)		13 (0.5)	36 (0.5)		49 (0.5)
Composite diabetes[g]								
Yes	36 (2.2)	100 (1.9)	64 (2.2)	.54	49 (2.0)	151 (2.0)	>.99	200 (2.0)
No	1563 (97.3)	5148 (97.6)	2836 (97.3)		2342 (97.4)	7205 (97.5)		9547 (97.5)
Missing	8 (0.5)	26 (0.5)	15 (0.5)		13 (0.5)	36 (0.5)		49 (0.5)
Composite hypertension[h]								
Yes	160 (10.0)	516 (9.8)	322 (11.1)	.19	223 (9.3)	775 (10.5)	.09	998 (10.1)
No	1438 (89.5)	4734 (89.8)	2582 (88.6)		2167 (90.1)	6587 (89.1)		8754 (89.4)
Missing	9 (0.6)	24 (0.5)	11 (0.4)		14 (0.6)	30 (0.4)		44 (0.5)
Probable PTSD								
Yes	322 (20.0)	520 (9.9)	173 (5.9)	<.001	327 (13.6)	688 (9.3)	<.001	1015 (10.4)
No	1276 (79.4)	4732 (89.7)	2733 (93.8)		2063 (85.8)	6678 (90.3)		8741 (89.2)
Missing	9 (0.6)	22 (0.4)	9 (0.3)		14 (0.6)	26 (0.4)		40 (0.4)
CVD events[i]								
Primary CVD outcome	92 (5.7)	267 (5.1)	130 (4.5)	.16	126 (5.2)	363 (4.9)	.52	489 (5.0)
All CVD	108 (6.7)	335 (6.4)	166 (5.7)	.33	160 (6.7)	449 (6.1)	.30	609 (6.2)
Length of follow-up								
Total, person-years	24 010	79 910	43 760	NA	36 663	111 017	NA	14 7680
Mean (SD), y	14.9 (2.7)	15.1 (2.5)	15.0 (2.7)		15.2 (2.3)	15.0 (2.7)		15.1(2.6)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; NA, not applicable; PTSD, posttraumatic stress disorder.

[a] Arrival group 1: arrived at the site in the morning of September 11, 2001; arrival group 2: arrived at the site in the afternoon of September 11; arrival groups 3 and 4: arrived at the site between September 12 and September 24.

[b] Duration group 1: worked at the site for 6 months or longer; duration group 2: worked at the site for less than 6 months.

[c] Determined using χ^2 analysis for categorical variables and analysis of variance for age.

[d] No missing data.

[e] See Additional Study Variables subsection of Methods for BMI category explanation.

[f] See Additional Study Variables subsection of Methods for hypercholesterolemia explanation.

[g] See Additional Study Variables subsection of Methods for diabetes definition.

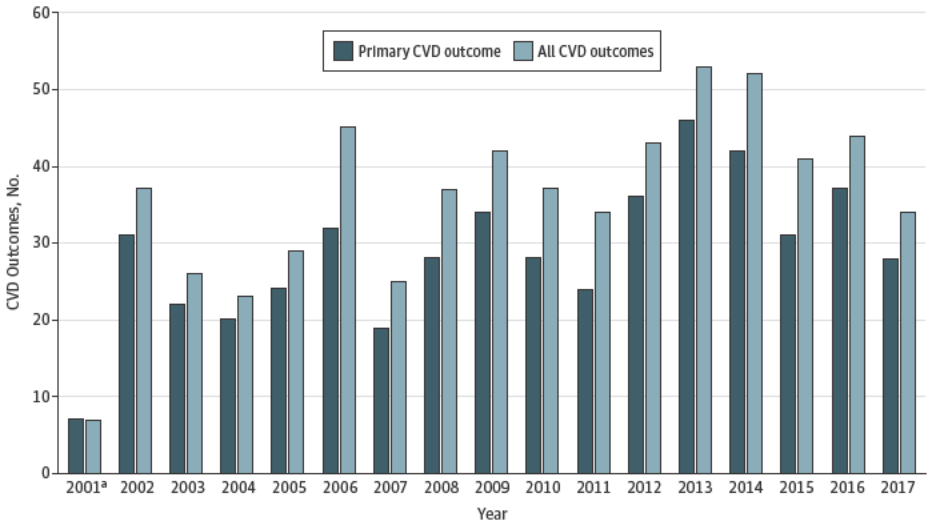
[h] See Additional Study Variables subsection of Methods for hypertension explanation.

[i] See CVD Outcomes subsection of Methods CVD events definition. All CVD includes CVD events in primary CVD outcome.

Schoenfeld residuals suggested that the Cox models met proportional hazards assumptions. **Figure 3** displays fully adjusted Cox models with arrival group as the measure of exposure and the primary CVD outcome. For arrival group 1 compared with arrival groups 3 and 4 combined, the minimally adjusted HRs of primary CVD were 1.39 (95% CI, 1.07-1.82; *P* = .02), and the fully adjusted HR of primary CVD was 1.44 (95% CI, 1.09-1.90; *P* = .01). The HRs for arrival group 2 vs arrival groups 3 and 4 were not significantly elevated. The *P* value for linear trend for the HRs of the 3 arrival group categories was *P* = .009 for fully adjusted models.

Well-established CVD risk factors, including hypertension (HR, 1.41; 95% CI, 1.10-1.80; *P* = .01), hypercholesterolemia (HR, 1.56; 95% CI, 1.28-1.91; *P* < .001), diabetes (HR, 1.99; 95% CI, 1.33-2.98; *P* = .001), smoking (current: HR, 2.13; 95% CI, 1.68-2.70; *P* < .001; former: HR, 1.55; 95% CI, 1.23-1.95; *P* < .001), and class I obesity (HR, 1.69; 95% CI, 1.13-2.54; *P* = .01), were associated with the primary CVD outcome in the arrival group multivariable analysis. These same risk factors were also associated with the primary CVD outcome in the duration group multivariable analysis. Neither BMI nor PTSD was significantly associated with the primary CVD outcome. No significant interactions of arrival group with other covariates were observed. For all-CVD variables, HRs for arrival groups 1 and 2 were modestly smaller than for the primary CVD outcome, but in the same direction. The *P* value for linear trend across the 3 arrival group categories for all CVD was *P* = .02 for the fully adjusted model.

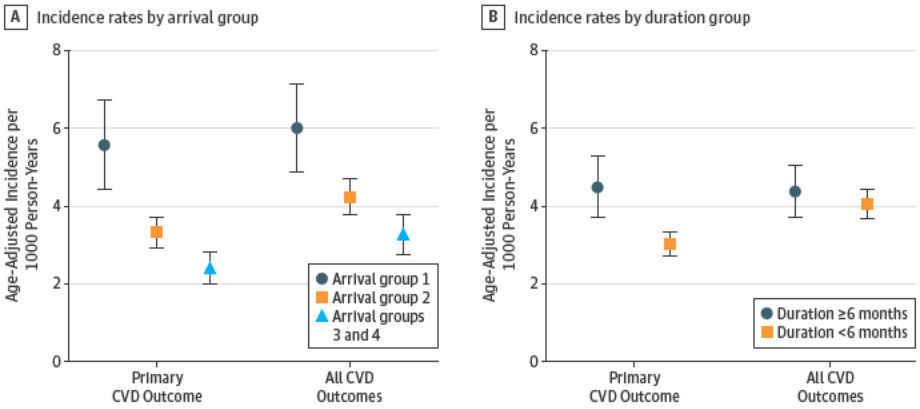
Figure 1. Cardiovascular Disease (CVD) Outcomes by Year



All CVD outcomes data include CVD events in primary CVD outcome.

[a] From September 11 to December 31, 2001.

Figure 2. Age-Adjusted Cardiovascular Disease (CVD) Incidence Rates



Incidence of CVD by arrival group (A) and duration group (B). The arrival groups are defined in the WTC Exposure subsection of the Methods section. Error bars indicate 95% CIs.

Hypertension, hypercholesterolemia, diabetes, smoking, and elevated BMI (preobesity, obesity class I, and obesity class III vs normal weight or underweight) showed significant associations with this outcome, while PTSD did not. Adjusted HRs for arrival groups were of similar magnitude to HRs for hypertension.

The fully adjusted Cox models using duration as the exposure measure and the primary CVD outcome are displayed in **Figure 4**. Hazard ratios for primary CVD for those present at the WTC site for 6 or more months vs those who worked less time at the site were 1.28 (95% CI, 1.04-1.57; *P* = .02) for minimally adjusted models and 1.30 (95% CI, 1.05-1.60; *P* = .02) for fully adjusted models. Results for the other covariates were similar to those in models using arrival group as the exposure. No significant interactions of duration with other covariates were observed. For all CVD, these HRs were 1.30 (95% CI, 1.09-1.56; *P* = .004) for minimally adjusted models and 1.31 (95% CI, 1.09-1.58; *P* = .005) for fully adjusted models.

In sensitivity analyses examining the CVD association with PTSD using PCL-17 scores only, the magnitude of the association was greater, although PTSD remained nonsignificant. For the primary CVD outcome, the HRs for PTSD were 1.19 (95% CI, 0.87-1.62; *P* = .27, arrival group model) and 1.24 (95% CI, 0.91-1.68; *P* = .18, duration model). The main associations between both acute and postacute work exposure variables with CVD were similar to those of the primary analyses.

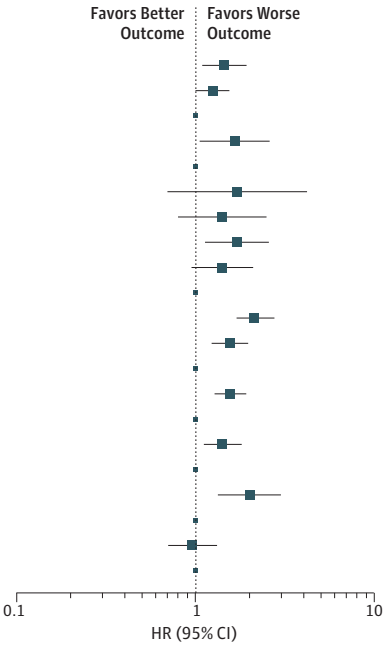
Discussion

We found statistically significant associations between acute (arrival group) and postacute (duration) work exposure at the WTC site and risk of CVD events throughout more than 16 years of follow-up. These associations were statistically significant after adjustment for age, race/ethnicity, and baseline assessments of BMI, hypertension, hypercholesterolemia, diabetes, smoking, and probable PTSD. Furthermore, the HR of the highest vs lowest exposure group was comparable in magnitude to that of hypertension, which is an established risk factor for CVD.

Traditional CVD risk factors include hypertension, hypercholesterolemia, diabetes, smoking, older age, and BMI. Environmental exposures to small, airborne particulate matter have increasingly

Figure 3. Primary Cardiovascular Disease Outcome Estimated Using the Fully Adjusted Cox Proportional Hazard Models With Arrival Group

Variable	HR (95% CI)	*P* Value
Arrival group 1: morning of 9/11	1.44 (1.09-1.90)	.01
Arrival group 2: afternoon of 9/11	1.24 (1-1.54)	.05
Arrival groups 3 and 4: 9/12-9/24		
Race: non-Hispanic white	1.64 (1.05-2.58)	.03
Race: other		
BMI category 5: obesity class III	1.70 (0.7-4.15)	.25
BMI category 4: obesity class II	1.41 (0.8-2.48)	.24
BMI category 3: obesity class I	1.69 (1.13-2.54)	.01
BMI category 2: preobesity	1.40 (0.95-2.07)	.09
BMI category 1: underweight/normal weight		
Cigarette smoking: current	2.13 (1.68-2.7)	<.001
Cigarette smoking: former	1.55 (1.23-1.95)	<.001
Cigarette smoking: never		
Hypercholesterolemia: yes	1.56 (1.28-1.91)	<.001
Hypercholesterolemia: no		
Hypertension: yes	1.41 (1.1-1.8)	.01
Hypertension: no		
Diabetes: yes	1.99 (1.33-2.98)	.001
Diabetes: no		
Probable PTSD: yes	0.96 (0.71-1.3)	.81
Probable PTSD: no		



9/11 indicates September 11, 2001; 9/12-9/24, between September 12 and September 24. Body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) category 1 indicates underweight or normal weight (BMI, ≤24.9); category 2, preobesity (25.0-29.9); category 3, obesity class I (30.0-34.9); category 4, obesity class II (35.0-39.9); and category 5, obesity class III (≥40.0). HR indicates hazard ratio; PTSD, posttraumatic stress disorder. Error bars indicate 95% CIs.

been recognized as also contributing to CVD risk, including by a 2004 American Heart Association scientific statement.[9] A 2010 update concluded that the body of evidence was "…consistent with a causal relationship between $PM_{2.5}$ [aerodynamic diameter] exposure and cardiovascular morbidity and mortality."[12(p1)]

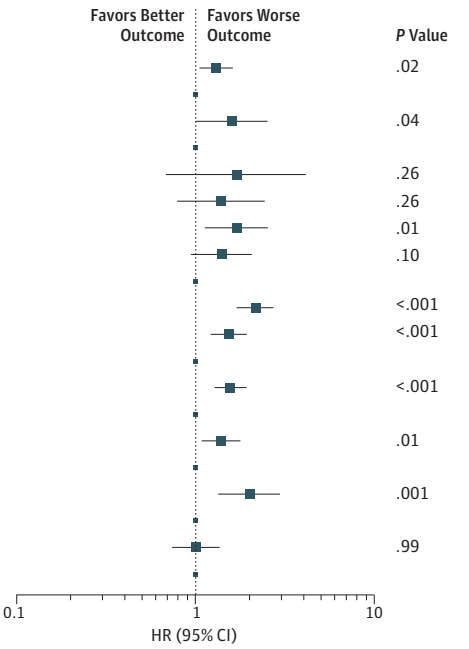
Previous non-WTC studies of air pollutants and CVD have focused on particulate matter less than 2.5 μm [$PM_{2.5}$], carbon monoxide levels, and ozone levels.[14,31-34] It is not possible to distinguish specific WTC dust components, which included an extensive variety from organic and inorganic material ranging in size from 2.5 μm or less to larger than 53 μm. In a measured sample, approximately 0.88% to 1.98% of the total mass was $PM_{2.5}$.[35] With more than a million tons of WTC dust, even 1% would constitute an enormous amount of $PM_{2.5}$. The highest concentration of dust occurred during and immediately after the collapse of the WTC towers, although dust became reaerosolized when disturbed during the recovery and cleanup effort.[36] Furthermore, there is the possibility of gaseous and chemical inhalations beyond concerns about particulate matter of specific sizes.

Ecologic studies of short-term exposures and acute CVD events typically link daily rates of measured particulate concentrations with concurrent CVD hospital admissions and deaths.[11,15] Similarly, ecologic studies of CVD events immediately following the WTC disaster showed significant associations with WTC exposure.[16-18] Potential mechanisms for short-term exposures and acute CVD outcomes may be different from mechanisms for longer-term exposures and CVD events occurring years later, since an event on the same or next day after exposure could more plausibly be linked to triggers related to pulmonary crises, stress-related spikes in blood pressure, or platelet aggregation.

Both high-level acute exposure with arrival before noon on 9/11 and recurrent postacute exposure with prolonged duration of work at the site were significantly associated with long-term risk of the primary CVD outcome and all CVD. We found the risk was 44% greater among firefighters who arrived on the morning of 9/11 compared with those who arrived later. This finding suggests that discrete exposure to dust and products of combustion could have initiated persistent pathologic processes related, in part, to chronic inflammation that increased CVD risk years later. Increased risk for other health outcomes has been noted in this cohort.[1-5] The association between WTC exposure

Figure 4. Primary Cardiovascular Disease Outcome Estimated Using the Fully Adjusted Cox Proportional Hazard Models With Duration Group

Variable	HR (95% CI)	*P* Value
Duration: ≥6 mo	1.30 (1.05-1.6)	.02
Duration: <6 mo		
Race: non-Hispanic white	1.59 (1.01-2.49)	.04
Race: other		
BMI category 5: obesity class III	1.68 (0.69-4.11)	.26
BMI category 4: obesity class II	1.38 (0.78-2.44)	.26
BMI category 3: obesity class I	1.69 (1.12-2.53)	.01
BMI category 2: preobesity	1.39 (0.94-2.05)	.10
BMI category 1: underweight/normal weight		
Cigarette smoking: current	2.15 (1.69-2.72)	<.001
Cigarette smoking: former	1.52 (1.21-1.92)	<.001
Cigarette smoking: never		
Hypercholesterolemia: yes	1.56 (1.27-1.91)	<.001
Hypercholesterolemia: no		
Hypertension: yes	1.38 (1.08-1.77)	.01
Hypertension: no		
Diabetes: yes	1.99 (1.33-2.98)	.001
Diabetes: no		
Probable PTSD: yes	1.00 (0.74-1.34)	.99
Probable PTSD: no		



Body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) category 1 indicates underweight or normal weight (BMI, ≤24.9); category 2, preobesity (25.0-29.9); category 3, obesity class I (30.0-34.9); category 4, obesity class II (35.0-39.9); and category 5, obesity class III (≥40.0). HR indicates hazard ratio; PTSD, posttraumatic stress disorder. Error bars indicate 95% CIs.

and CVD has also been observed in other WTC studies,[19] although not in all.[20-22] This difference may be owing to the high exposure levels experienced by FDNY firefighters compared with levels experienced by non-FDNY rescue and recovery workers. In a non-WTC study of the aftermath of an oil spill, those who worked on the cleanup for more than 180 days—similar to our duration exposure measure—showed a significantly greater long-term incidence of heart disease.[37]

Previous research from other WTC cohorts has shown an association between PTSD and CVD events.[21,38] Although we included PTSD in our models, we did not observe a significant association with either CVD outcome measure. We performed a sensitivity analysis because we were concerned that the timing of our PTSD measure, obtained from the earliest post-9/11 survey, may have contributed to the observed lack of significance. Sensitivity analyses examined the association of PTSD as measured after 2006 (using PCL-17 score) with CVD; however, PTSD still did not achieve statistical significance. Future research will study the possibility that PTSD measured later during follow-up could act as a mediator between WTC exposure and CVD.

Limitations and Strengths

This study has several limitations. Our exposure variables are relative and do not quantify specific concentrations of $PM_{2.5}$ or other dust components. Similarly, work records were not available to determine the exact time of arrival or days of work at the site. Nonetheless, the measures we used have demonstrated external validity in studies of lung function decline, adverse pulmonary symptoms, and PTSD.[1,4,5,29] In addition, hospital records were not available in all cases to confirm CVD outcomes, so misclassification is possible. However, the severity of these diagnoses is such that our program physicians typically require supporting documentation. Similarly, lack of the exact date of a CVD event can be expected to reduce precision of HR estimates, which would likely bias toward the null. It is possible that the long-term risk of CVD observed in these firefighters can be attributed to their stressful occupation, which also reexposed them to smoke and dust in subsequent fires. However, in this analysis, the reference groups were firefighters who likely had similar non-WTC exposures. The reference groups were still WTC exposed, albeit less exposed, rather than non-WTC exposed, suggesting that the true association of exposure might be greater than we observed.

This study also has considerable strengths. The FDNY WTC-exposed firefighter cohort, established before 9/11, has been extensively studied with consistency of results. At baseline, the few (<0.5%) participants with CVD were removed from analyses, leaving a healthy group that was followed up for as long as 16 years. The CVD outcomes were based on physician-documented diagnoses in the FDNY medical record rather than patient self-report that others have used.[22,38] These diagnoses, along with physicians' notes, were clinically reviewed for classification as primary outcome events or all-CVD events. In addition, CVD diagnoses are not conditions whose medical care is covered under the James Zadroga 9/11 Health and Compensation Act. As a result, the likelihood of overreporting CVD for purposes of compensation is small. Furthermore, we observed associations of the traditional CVD risk factors consistent with what is known, possibly providing further evidence of external validity.

Conclusions

We observed that acute WTC dust exposure, as well as repeated exposures over the months of cleanup, may be associated with elevated CVD risk throughout 16 years of longitudinal follow-up. The findings appear to reinforce the importance of long-term monitoring of the health of survivors of disasters. Future studies are warranted to address whether identifying and addressing changes in other CVD risk factors can mitigate elevated CVD risk associated with disaster exposure.

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Corresponding Author: Rachel Zeig-Owens, DrPH, MPH, Fire Department of the City of New York, 9 MetroTech Center, Brooklyn, NY 11201 (rachel.zeig-owens@fdny.nyc.gov).

Author Affiliations: Division of Epidemiology, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York (Cohen, Zeig-Owens); The Bureau of Health Services and the Fire Department of the City of New York World Trade Center Health Program, Fire Department of the City of New York, Brooklyn, New York (Zeig-Owens, Joe, Webber, Weiden, Jaber, Skerker, Yip, Schwartz, Prezant); Pulmonary Medicine Division, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York (Zeig-Owens, Joe, Cleven, Skerker, Yip, Schwartz, Prezant); Division of Biostatistics, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York (Hall); Department of Epidemiology and Population Health, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York (Webber); Pulmonary, Critical Care, and Sleep Medicine Division, Department of Medicine, New York University School of Medicine, New York (Weiden); Pulmonary, Critical Care, and Sleep Medicine Division, Department of Environmental Medicine, New York University School of Medicine, New York (Weiden).

Author Contributions: Drs Cohen and Zeig-Owens contributed equally to the investigation. Drs Zeig-Owens and Prezant had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Cohen, Zeig-Owens, Hall, Webber, Weiden, Prezant.

Acquisition, analysis, or interpretation of data: Cohen, Zeig-Owens, Joe, Hall, Webber, Weiden, Cleven, Jaber, Skerker, Yip, Schwartz, Prezant.

Drafting of the manuscript: Cohen, Zeig-Owens, Joe, Weiden.

Critical revision of the manuscript for important intellectual content: Cohen, Zeig-Owens, Hall, Webber, Weiden, Cleven, Jaber, Skerker, Yip, Schwartz, Prezant.

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EDITORIAL

Coronary microvascular disease: the next frontier for *Cardiovascular Research*

Colin Berry [1,2]* and **Dirk J. Duncker** [3,4]

[1]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK; [2]Department of Cardiology, Golden Jubilee National Hospital, Clydebank, UK; [3]Division of Experimental Cardiology, Department of Cardiology, Thoraxcenter, Cardiovascular Research School COEUR, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; and [4]Netherlands Heart Institute, Utrecht, The Netherlands

Introduction

Ischaemic heart disease (IHD) persists as the leading cause of premature death and disability worldwide.[1] IHD may present as acute myocardial infarction (MI) or a chronic coronary syndrome.[2] IHD is increasingly recognized as a concomitant problem in systemic health problems, such as rheumatoid arthritis. Coronary atherosclerosis is a major cause of IHD. The historical primacy of coronary artery disease (CAD) leads some clinicians to view coronary heart disease (CHD) and IHD as synonymous, interchangeable terms. Emerging clinical evidence indicates this is far from being the case and a major reappraisal is warranted.[3] CHD represents a subset of IHD, and these terms should not be used interchangeably.

Under-recognition of coronary microvascular disease: time for a reappraisal

Coronary microvascular dysfunction (CMD) has, historically, been under-recognized, not least since the microvessels are invisible to currently available clinical imaging techniques. This simple issue has underpinned key misconceptions about IHD and major knowledge gaps relating to CMD.[3] Atherosclerosis is the major cause of CHD and the pathogenesis, prognosis, and treatment of these problems are well-established.[2] In recent years, new insights into the causes and consequences of IHD have called into question the CAD stenosis-centred/CHD paradigm.

Most recently, the ISCHEMIA trial results were reported at the Scientific Sessions of the American Heart Association (16 November 2019) (https://professional.heart.org/professional/ScienceNews/UCM_505226_ISCHEMIA-Clinical-Trial-Details.jsp).[4] The central hypothesis of the ISCHEMIA trial was that in patients with angina and moderate–severe myocardial ischaemia, compared with initial non-invasive, medical management, a routine invasive strategy with cardiac catheterization followed by coronary revascularization plus optimal medical therapy, would improve prognosis. After 3.3 years of follow-up, there was no difference in the primary endpoint between the randomized groups.[4] This trial did have limitations. Under-recruitment and a lower than expected event rate reduced the statistical power for analysis of the primary outcome that ultimately led to a belated, yet prespecified change in the primary composite outcome. Longer-term follow-up with accrual of more events may provide new insights. Nonetheless, ISCHEMIA is the largest study of its kind, and the results call into question the benefits of coronary revascularization in patients with myocardial ischaemia. Crucially, it questions the stenosis-centred pathophysiology of IHD and warrants reassessment of the role of CMD in IHD.

Clinical relevance of coronary microvascular dysfunction

CMD is increasingly implicated as a relevant cause of IHD.[4] Angina secondary to myocardial ischaemia may occur in patients with no obstructive CAD (INOCA). In fact, fewer than one in five patients presenting with known or suspected angina have obstructive CAD, as revealed by anatomical imaging with computed tomography coronary angiography (CTCA)[5] (*Figure 1*). In the clinic, the cause of the angina is uncertain in the majority of affected patients, most of whom are women.[5,6] This becomes all the more relevant given that CTCA-guided management leads to worse angina and quality of life overall, contrary to what might be anticipated.[7] The Coronary Microvascular Function and CT Coronary Angiogram (CorCTCA) study is currently examining the prevalence and clinical significance of CMD in patients with angina but no obstructive CAD, as defined by CTCA.[8] The recent Coronary Microvascular Angina (CorMicA trial) served evidence that undertaking tests of coronary vascular function during clinically indicated coronary angiography identifies relevant endotypes (microvascular angina, vasospastic angina, and non-cardiac chest pain) and targeted therapy was associated with improvements in angina and quality of life at 6-[9] and 12 months.[10] Considering acute MI, about 1 in 10 patients presenting with MI have no obstructive coronary arteries (MINOCA).[11] Microvascular and vasospastic disease are also implicated. Considering the natural history, INOCA and MINOCA may underlie the development of heart failure with preserved ejection fraction[12] which is an increasingly recognized, prevalent cause of heart failure.

Coronary microvascular disease may be part of a systemic continuum of microvascular disease, with multiple affected organ beds.[13] Small vessel disease in the heart and brain links INOCA with vascular dementia.[13] The deleterious effects of vascular risk factors, such as hypertension, obesity, smoking, and diabetes are relevant, and genetic associations,[14] notably leading to increased exposure to endothelin-1[15] are also

* Corresponding author. Tel: +44 (0)141 330 3325, +44 (0)141 951 5000; fax: +44 (0)141 330 6794, E-mail: colin.berry@glasgow.ac.uk

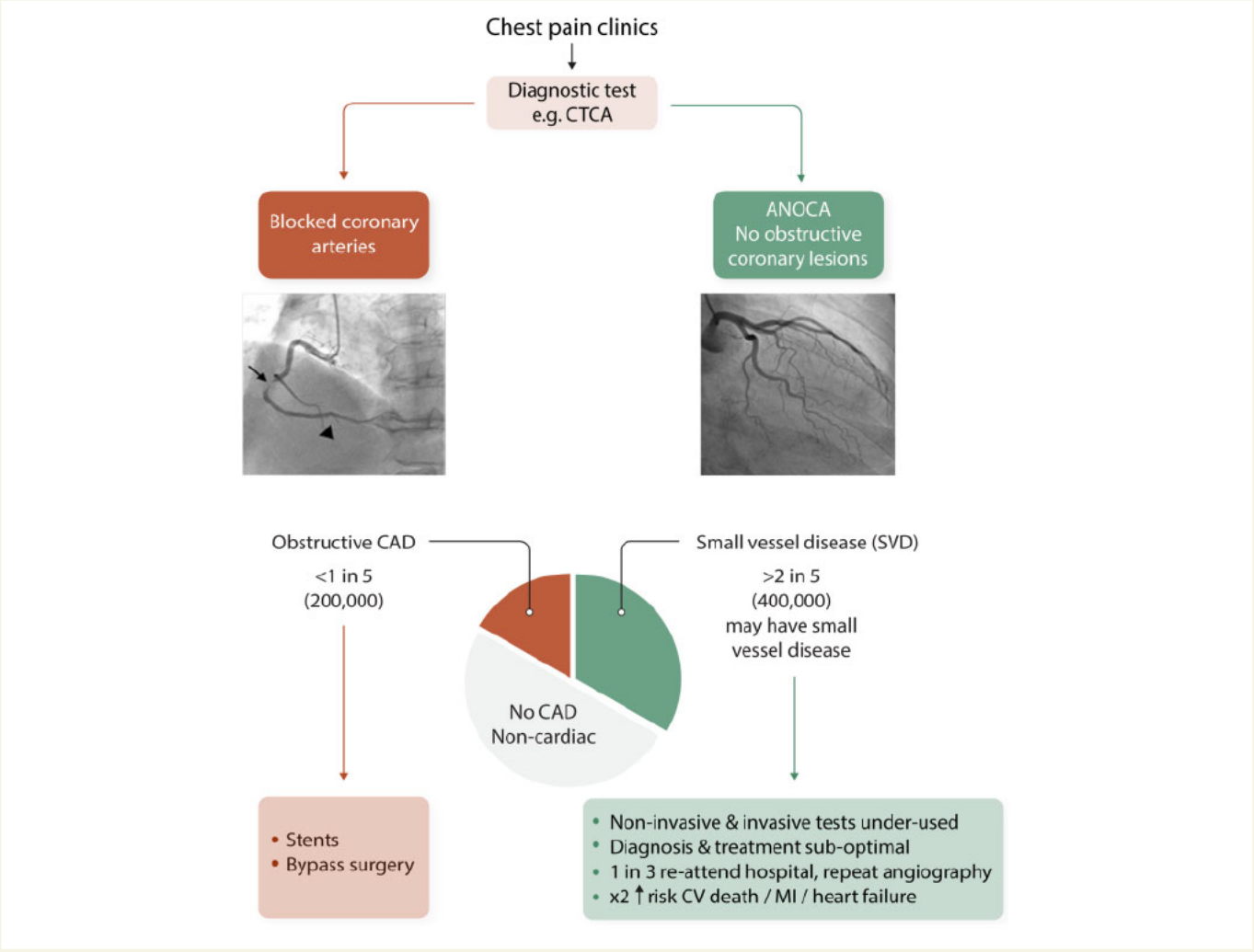

Figure 1 Ischaemic heart disease endotypes. ANOCA, angina with no obstructive coronary arteries; CAD, coronary artery disease; CTCA, computed tomography coronary angiography; CV, cardiovascular; MI, myocardial infarction.

implicated. CMD is causally implicated in multiple systemic conditions including the cardiotoxicity of chemotherapy, systemic inflammatory conditions, such as rheumatoid arthritis, heart failure, and pregnancy.[16] Sex associations are also relevant.[17] Obstructive CAD typically associates with male sex, whereas small vessel disease associates with female sex.[5,6,8,9] Since anatomical imaging with CTCA is diagnostically most useful for identifying and excluding CAD and compared with ischaemia testing, least useful for the diagnosis of CMD, an all-comers strategy based on CTCA introduces a sex bias.[3] Under-recognition and under-treatment of heart disease in women is a hot topic[16,17] and more research seems warranted.

Some of the persisting, clinically relevant questions are: (i) In INOCA and MINOCA, is myocardial ischaemia the consequence and/or cause of microvascular dysfunction? (ii) Is chronic myocardial ischaemia therapeutically modifiable? (iii) Is microvascular dysfunction a common problem after successful revascularization? (iv) If so, what are the mechanisms underlying microvascular dysfunction, what treatments might be disease-modifying and beneficial to patients? (v) Is CMD a modifiable therapeutic target? (vi) What is the natural history of CMD? The clinical relevance of microvascular dysfunction in patients with flow-limiting CAD is being investigated in the DEFINE-FLOW study[18] due to be reported in 2020. The Changes in Ischemia and Angina Over 1 Year Among ISCHEMIA Trial Screen Failures With no Obstructive CAD on Coronary CT Angiography (CIAO) substudy will also be informative.[19]

Coronary microvascular dysfunction in the spotlight

Accordingly, CMD has generated substantial interest in the clinical and basic science communities in recent years. This Spotlight Issue brings together internationally leading thought-leaders, researchers, and their trainees. The authors have a broad range of backgrounds including basic science, translational research, and clinical studies. Their remit is to focus on 'hot topics' in CMD and give perspectives on the science.

The Spotlight Issue begins with a Position Paper, 'Coronary Microvascular Dysfunction in Cardiovascular Disease', from the European Society of Cardiology (ESC) Working Group on Coronary Pathophysiology and the Microcirculation.[20] The Position Paper by Drs Padro, Manfrini, Badimon, and coauthors highlights, firstly, updated evidence on the pathophysiological consequences of microvascular

dysfunction in the heart. Secondly, they focus on the relevance of cardiovascular risk factors and comorbid conditions for microcirculatory dysfunction. Thirdly, they highlight the clinical consequences of CMD, which is not a benign problem. They conclude that clinical strategies should prioritize detection of CMD which in turn will help in the stratification of cardiovascular in support of precision medicine.

The first review article focuses on experimental models of CMD. Sorop *et al.*[21] discuss the benefits and pitfalls of existing small and large animal models of CMD, with a specific focus on metabolic disturbances which may be experimentally induced or spontaneous. They provide a comprehensive description of relevant experimental research involving a range of species. They also highlight the value of experimental models for identifying novel therapeutic targets and for the subsequent development and testing of novel therapeutic interventions.

The next article focuses on 'Diagnosis of coronary microvascular dysfunction in the clinic'. Ong *et al.*[22] cover the diagnosis of CMD in an article that discusses the invasive and non-invasive methods for the assessment of CMD in humans. They highlight an integrative approach for assessing coronary vascular function using a diagnostic guidewire initially and then pharmacological reactivity testing using intracoronary administration of acetylcholine (ACh). They highlight the *Interventional Diagnostic Procedure* developed by Berry and Ford[9] as the current gold standard for assessing coronary vascular function. A review from Bairey Merz *et al.*[23] on 'Treatment of CMD', provides a comprehensive overview of pharmacotherapies with potential efficacy in alleviating CMD. The article highlights pivotal clinical trials in CMD, such as CorMicA[9] and WARRIOR (ClinicalTrials.gov Identifier: NCT03417388). In addition, they highlight novel therapeutics, including gene and cell-based therapies.

The Spotlight also includes articles on CMD in different cardiovascular disease settings. Sechtem *et al.*[24] focus on CMD in stable IHD, including INOCA and obstructive CAD. They focus on challenging concepts including CMD in the absence of atherosclerosis, CMD detection, microvascular spasm, collateral connections, and the prognostic importance of global coronary flow reserve. Konijnenberg *et al.*[25] focus on the pathophysiology and diagnosis of CMD in acute MI. The authors state that the current standard of care, primary percutaneous coronary intervention, successfully restores coronary blood flow in the vast majority of patients yet most also have evidence of failed myocardial perfusion, revealed as microvascular obstruction (MVO) using magnetic resonance imaging. MVO confers an adverse prognosis and in spite of multiple therapeutic trials, MVO has no evidence-based treatment and has an unmet therapeutic need. The manuscript also discusses pre-clinical models. Camici *et al.*[26] discuss the mechanisms by which CMD is a contributing factor to the transition from left ventricular hypertrophy to heart failure with either a reduced or preserved ejection fraction. Relevant mechanisms are discussed. CMD in genetic cardiomyopathy is also described. Konst *et al.*[27] describe the pathogenic role of CMD in the setting of other cardiac or systemic conditions. They highlight diabetes mellitus, obesity, and vascular inflammation as relevant causes of CMD.

A further disease modifier of CMD pathology is sex.[16,17] Women who are under investigation for myocardial ischaemia are more likely to have non-obstructive CAD on coronary angiography and CMD is relevant. In the final article of this Spotlight Issue, Waheed *et al.*[28] explore sex associations of INOCA, MINOCA, symptoms, risk factors and, intriguingly, sex-specific factors such as inflammation, mental stress, autonomic, and neuro-endocrine dysfunction that may cause women—relative to men—to be more likely to develop CMD. Sex differences have major implications for both diagnosis and treatment of cardiovascular disease.

We recognize and thank experts from the COVADIS (Coronary Vasomotor Disorders International Study Group) and ESC Working Group on Coronary Pathophysiology and Microcirculation for their collaboration. The Editors hope that by bringing this collection of articles together, the Spotlight will enhance interest for research in CMD. This problem pervades human disease, mechanisms are poorly understood and specific treatments are lacking. CMD presents an exciting field for discovery and translation to reduce the unmet therapeutic need.

Conflict of interest: C.B. is employed by the University of Glasgow which holds consultancy and research agreements with companies that have commercial interests in the diagnosis and treatment of ischaemic heart disease. The companies include Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GSK, HeartFlow, Menarini, Novartis, and Siemens Healthcare. These companies had no involvement in this manuscript. D.J.D. serves *ad hoc* as a consultant for Medtronic and Sanofi-Aventis. These companies had no involvement in this manuscript.

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Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

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

Molly Remch*
Zoey Laskaris, MPH*
Janine Flory, PhD
Consuelo Mora-McLaughlin
Alfredo Morabia, MD, PhD

BACKGROUND: We sought to determine whether post-traumatic stress disorder (PTSD) is a risk factor for myocardial infarction (MI) and stroke, beyond the expected effects from recognized cardiovascular risk factors and depression.

METHODS AND RESULTS: World Trade Center–Heart is an observational prospective cohort study of 6481 blue-collar first responders nested within the World Trade Center Health Program in New York City. Baseline measures in 2012 and 2013 included blood pressure, weight and height, and blood lipids. PTSD, depression, smoking, and dust exposure during the 2001 cleanup were self-reported. During the 4-year follow-up, outcomes were assessed through (1) interview-based incident, nonfatal MI, and stroke, validated in medical charts (n=118); and (2) hospitalizations for MI and stroke for New York city and state residents (n=180). Prevalence of PTSD was 19.9% in men and 25.9% in women, that is, at least twice that of the general population. Cumulative incidence of MI or stroke was consistently larger for men or women with PTSD across follow-up. Adjusted hazard ratios (HRs) were 2.22 (95% confidence interval [CI], 1.30–3.82) for MI and 2.51 (95% CI, 1.39–4.57) for stroke. For pooled MI and stroke, adjusted HRs were 2.35 (95% CI, 1.57–3.52) in all and 1.88 (95% CI, 1.01–3.49) in men free of depression. Using hospitalization registry data, adjusted HRs were 2.17 (95% CI, 1.41–3.32) for MI; 3.01 (95% CI, 1.84–4.93) for stroke; and for pooled MI and stroke, the adjusted HR was 2.40 (95% CI, 1.73–3.34) in all, HR was 2.44 (95% CI, 1.05–5.55) in women, and adjusted HR was 2.27 (95% CI, 1.41–3.67) in men free of depression. World Trade Center dust exposure had no effect.

CONCLUSIONS: This cohort study confirms that PTSD is a risk factor for MI and stroke of similar magnitude in men and women, independent of depression.

*M. Remch and Z. Laskaris contributed equally to this work as first authors.

Key Words: air pollution ■ depression ■ disasters ■ myocardial infarction ■ stress disorders, post-traumatic ■ stroke

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WHAT IS KNOWN

- Post-traumatic stress disorder has been consistently shown to be an independent risk factor for incident myocardial infarction or stroke in cohort studies.
- However, despite the wealth of evidence, post-traumatic stress disorder is still not recognized as a risk factor for cardiovascular disease because available studies are all affected by 1 or several limitations.

WHAT THE STUDY ADDS

- World Trade Center–Heart offers unique and strong evidence that World Trade Center attack–related post-traumatic stress disorder is a risk factor for myocardial infarction and stroke, in men and women, and independent of recognized cardiovascular risk factors and depression.
- Because of its methodological strength (ie, active follow-up, medical chart validation, and adjustment for depression), this study validates previous reports of exclusively male or female cohorts.

This is the first report from World Trade Center (WTC)-Heart—a cohort study specifically designed to assess the association between early response to the WTC September 11 attack and cardiovascular outcomes. WTC-Heart comprises blue-collar workers who were involved in the cleaning of the debris of the WTC complex during the months immediately after the attack. The cohort offers the ability to assess whether post-traumatic stress disorder (PTSD) is involved in cardiovascular disease (CVD) incidence because of 3 cohort characteristics: (1) it underwent the same, extraordinary traumatic event at a discrete point in time and suffers from an excess burden of PTSD symptoms at least twice that of the general population[1,2]; (2) being nested within a long-term program offering free care to first responders, can explore long-term risk 11 to 15 years after the event; and (3) because first responders were on average in their forties in 2001, it is a relatively young cohort in which CVDs would be expected to be rare if it was not because of this unique exposure to the psychologically and environmentally traumatic event in 2001.

PTSD—a syndrome characterized by re-experiencing the traumatic exposure, avoidance of reminders, hyperarousal, and negative mood and cognitions, highly prevalent among WTC responders[3]—has been consistently shown to be an independent risk factor for incident myocardial infarction (MI) or stroke in cohort studies.[4–10] Previous reports from a different WTC cohort have related psychological stress to heart diseases among people who worked at or were living in the vicinity of Ground Zero in 2001 to 2002.[11,12] However, despite the wealth of evidence, PTSD is still not recognized as a risk factor for CVD because available studies are all affected by 1 or several limitations, such as self-report of established CVD risk factors (eg, lipids, blood pressure, weight, and height), self-reported CVD events, exclusively male or female cohorts, or nonadjustment for depression. In contrast, in WTC-Heart, CVD risk factors were measured in a standardized fashion, and incident cases of MI and stroke were assessed using an active follow-up, including personal interviews and validation of events in medical charts simultaneously in men and women.

METHODS

The data, analytic methods, and study materials will not be automatically made available to other researchers for purposes of reproducing the results or replicating the procedure. The cohort is nested within the WTC Health Program (WTCHP), and authorization will have to be obtained from the WTCHP too.

WTC-Heart is a prospective, fixed cohort of 6481 WTC first responders involved in cleaning up the debris of the WTC complex in New York City in 2001 and 2002 and recruited within the WTCHP. Active follow-up for incident and recurrent CVD was conducted from January 2012 until June 2016, remotely via e-mail, mail, and phone interviews in English, Spanish, and Polish. The cohort was also linked with the New York state hospitalization database, SPARCS.

The cohort was recruited from 2 WTCHP sites (ie, the Icahn School of Medicine at Mount Sinai or North Shore Long Island Jewish Hospital) in New York City. The WTCHP, established in 2002, comprises nonfirefighter workers and volunteers engaged in rescue, recovery, restoration of services, cleanup, or other support work on or after September 11. These first responders were eligible in the WTCHP if they had worked for ≥4 hours on September 11 to 14, 2001, ≥24 hours during the month of September 2001, or ≥80 hours total during the period of October through December 2001.[13] Also eligible were employees of the Office of the Chief Medical Examiner who processed human remains, of the Port Authority Trans-Hudson Corporation who participated in the cleanup efforts for ≥24 hours from February to July 2002, and workers who drove, repaired, cleaned, or maintained vehicles that handled WTC debris for at least 1 day between September 11, 2001, and July 31, 2002.[14]

Sample

The cohort is a consecutive sample of 6481 women and men attending one of their annual clinical visits, up to their 10th annual visit, at the WTCHP between January 2012 and June 2013 (baseline). Annual visits are not necessarily associated with medical problems requiring care. Informed consent was provided on the day of recruitment, in English, Spanish, and Polish. The Queens College Institutional Review Board and those of the 2 recruitment sites approved the WTC-Heart protocol.

Exposures

Recognized cardiovascular risk factors comprised: (1) standardized 2 measurements of blood pressure to the third digit

(eg, 12.2) after sitting down; (2) a comprehensive smoking history; (3) body weight and height measured in lightly dressed subjects; and (4) blood lipids: total cholesterol, low-density lipoprotein, and triglycerides. Clinical personnel were trained specifically for this study and provided identical, new instruments (scales, sphygmomanometers). Baseline mental health symptoms included the PTSD checklist PCL-C (civilian) for DSM-IV,[15] with a specific preamble relating the answers to the participation in the WTC cleanup. The cutoff for probable PTSD was ≥44 points as recommended given the prevalence of PTSD in the cohort.[16] Possible depression was defined as a score of ≥10 (in a range of 0–27) on the 9 questions of the Patient Health Questionnaire-9.[17]

In a detailed questionnaire, each participant indicated: (1) which day on or after September 11 they began working on the WTC complex; (2) whether they were directly in the cloud of dust (or blackout) from the collapse of the WTC buildings or not; (3) whether their work was adjacent or on the pile or pit, terms that referred to the former location of the twin towers of the WTC complex; and (4) whether they wore a protective mask.[18]

Active Follow-Up

Attempts were made to contact every participant once a year from the 2012 baseline to June 2016. At each annual contact, incident cardiac and incident neurological events were reported in a standardized, self-administered survey in English, Spanish, and Polish either online, by mail, or by telephone. In case of death reported by a relative or by the WTCHP, a questionnaire and request of death certificate was mailed to either relatives or healthcare provider.

Outcomes

All self-reported CV events on the follow-up forms, including positive report of cardiac symptoms, MI, neurological symptoms, or stroke, were tentatively confirmed by specific additional personal interviews conducted by phone by trained interviewers in English, Spanish, or Polish. Determination of incident and recurrent cardiovascular outcomes in medical charts was performed by a blinded adjudicating panel comprising the principal investigator (A.M.) and a senior research worker (C.M.-M.) with 24 years of experience adjudicating acute MI and stroke in several large population-based studies. An MI was confirmed in the presence of typical symptoms, EKG signs, troponin, and enzymatic movement. A stroke or a transient ischemic attack was confirmed in the presence of typical symptoms and medical imaging or sonographic signs.

From January 1, 2012, through December 31, 2016, (the latest year available) all WTC-Heart participants were electronically linked to New York State Department of Health SPARCS program, which includes diagnoses and dates for all patients discharged from acute care hospitals, excluding psychiatric and federal hospitals. The coding of discharge diagnoses may not be accurate, but the degree of inaccuracy is likely to be homogeneous across the cohort. Matched records had identical key identifying information, such as name, date of birth, last 4 digits of the social security number, or address. Analyses were restricted to the 5484 New York city or state residents. We used, for MI, *International Classification of Diseases, Ninth Revision* codes 410 to 411 and *International Classification of Diseases, Tenth Revision* codes I21-I22, and for stroke, *International Classification of Diseases, Ninth Revision* codes 430 to 432 and *International Classification of Diseases, Tenth Revision* codes I60-I63. For the follow-up years 2012 through 2016, 180 WTC-Heart study participants were identified in the SPARCS database as having been hospitalized with a discharge diagnosis of MI or stroke.

Statistical Analysis

Kaplan-Meier survival analysis was used to plot the cumulative incidence of MIs and stroke. Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of MI or stroke, adjusted for use of a respirator and for recognized cardiovascular risk factors: age, blood pressure, total cholesterol, body mass index, tobacco use, and, when relevant, sex. Firth procedure was applied to improve aHR and CI estimates from Cox proportional hazard models with small sample sizes and few measured outcome events.[19]

Because PTSD may have increased weight gain, tobacco use, blood pressure, and possibly cholesterol after the 2001 to 2002 trauma, resulting in these factors being on the pathway to MI and stroke and biasing the hazard ratios (HRs) toward the null, we present primary analyses both age adjusted and, when sample size allows, adjusted for all these factors.

Time of event was retrieved from the participant's interview or SPARCS records. For event-free participants censoring for interview-based incident, events occurred at the date of completion of the most recent annual survey, or, for SPARCS-derived events, on December 31, 2016—the last date of available SPARCS data. Analyses of postbaseline, incident outcomes were, therefore, repeated including and excluding MIs and strokes recurring during follow-up among subjects who already had an MI or stroke before 2012. We report the analysis including all cases in the article for 4 reasons: (1) because this cohort had a mean age of 51 years in 2012, all cardiovascular events occurred after 2001; (2) PTSD is a chronic disease, most likely secondary to 2001, for which it is difficult to set an exact date of onset; (3) these middle aged subjects who had cardiovascular events before baseline were subjects at the highest risk in the cohort and excluding them would also introduce selection bias; (4) removing 35 recurrent cases did not alter the statistical power for the full analysis (as shown in the article) but left thin data for the sex- and disease-specific analyses. Thus, subjects who had had prebaseline cardiovascular events were excluded for some of the exploratory full sample analyses but kept in all other analyses, with only the postbaseline events going into the numerator of the hazard rates and risks.

MI and stroke were analyzed both separately and pooled as a single outcome (MI/stroke) because separate analyses of self-reported MI and stroke, provided in an appendix, yielded associations of consistent magnitudes. Similarly, men and women were analyzed estimating both separate and pooled sex-adjusted HRs. The number of female cases (9 MIs, 7 strokes, and 22 hospitalizations for MI or stroke) precluded statistical power for most analyses, but, as shown in the appendix, the magnitude of the associations was remarkably consistent across sex allowing for meaningful sex-adjusted

HRs. The participants who had both MI and stroke were analyzed as per the first of the 2 outcomes in the analyses pooling MI and stroke.

Because PTSD and depression are highly correlated, the analyses for pooled MI and stroke adjusted for recognized cardiovascular risk factors were repeated among 4120 nondepressed men (the number of female cases was too small to perform sex-adjusted analyses), after exclusion of men having either depression only (n=97), depression and PTSD (n=477), or missing depression data (n=248).

RESULTS

The sociodemographic, cardiovascular, and mental characteristics of the WTC-Heart cohort were similar to those of the whole WTCHP in which it was nested (Table I in the Data Supplement). As of July 1, 2016, 510 participants (7.9%) had no follow-up information. The analyses are, therefore, based on 4942 men and 1029 women (n=5971).

Baseline (2012–2013) Characteristics

Mean age was 51.3 years in men and 51.1 years in women. The cohort was 82.8% men, 54.1% white, and 25.4% lower than college education. The Table shows these characteristics by sex. Prevalence of PTSD was 19.9% in men and 25.9% in women.

Recognized Cardiovascular Risk Factors and Dust

Figure 1 and Table II in the Data Supplement show current smoking standing out—besides PTSD not shown in Figure 1—as the main recognized risk determinant of incident (including recurrent) pooled MI and stroke, after adjustment for other cardiovascular risk factors and PTSD. Specific results for MI or stroke are shown in Tables III and IV in the Data Supplement. Moreover, resting heart rate per minute at baseline was, respectively, for those without and with PTSD, 68.9 and 70.8 in men and 69.5 and 69.9 in women (not shown in a table).

None of the variables differently expressing the timing or intensity of exposure to the WTC dust and dust cloud were independently associated with subsequent MI or stroke in these analyses (Table V in the Data Supplement). Donning of a protective mask was deemed the closest approximation of the amount of dust inhaled and was adjusted for in all multivariate analyses (Figure 1).

Cumulative Risk of CVD by PTSD

By June 30, 2016, reported cases were 70 MIs, of which 20 were recurrent, and 53 strokes, of which 15 were recurrent. Figure 2 shows the cumulative risks of MI and stroke for the whole sample by PTSD status. The curves diverge early, divergence increases over time, with statistically significant differences at $P<0.0001$. Specific

Table. Baseline Characteristics of Men and Women Comprising the World Trade Center–Heart Cohort (n=5971)—New York, 2012 to 2016

Characteristics	Categories	Men		Women	
		n	%	n	%
Total		4942	100	1029	100
Race	White	2857	57.8	372	36.2
	Black	669	13.5	240	23.3
	Missing	1141	23.1	348	33.8
Ethnicity	Hispanic	1338	27.1	432	42.0
	Missing	96	1.9	19	1.9
Responder	Trained	2077	42.0	424	41.2
	Nontraditional	2359	47.7	517	50.2
	Missing	506	10.2	88	8.6
Smoking	Never	2688	54.4	611	59.4
	Current	351	7.1	64	6.2
	Former	1383	28.0	240	23.2
	Missing	520	10.5	114	11.1
Protective mask on September 11	Donned	4334	87.7	825	80.1
	Missing	99	2.0	23	2.2
Blood pressure	High (systolic >140 or diastolic >90 mm Hg)	1098	22.2	124	12.1
	Missing	143	2.9	47	4.6
Total cholesterol	High (>6.2 mmol/L)	517	10.5	146	14.2
	Missing	NA	NA	NA	NA
HDL	Low (men, <1 mmol/L; women, <1.3 mmol/L)	1069	21.6	527	51.2
	Missing	608	12.3	115	11.2
BMI	Normal (<25 kg/m^3)	458	9.3	258	25.1
	Overweight (25–29.9 kg/m^2)	2012	40.7	382	37.1
	Obese (30+ kg/m^2)	2472	50.0	389	37.8
	Missing	NA	NA	NA	NA
PTSD	Yes	984	19.9	266	25.9
	Missing	NA	NA	NA	NA
Depression	Yes	574	11.6	185	18.0
	Missing	248	5.0	59	5.7
Menopause	Yes	…	…	420	40.8
	Missing	…	…	2	0.2
Education	College graduates	1319	26.7	379	36.8
	Missing	570	11.5	112	10.9

BMI indicates body mass index; HDL, high-density lipoprotein; NA, not available; and PTSD, post-traumatic stress disorder.

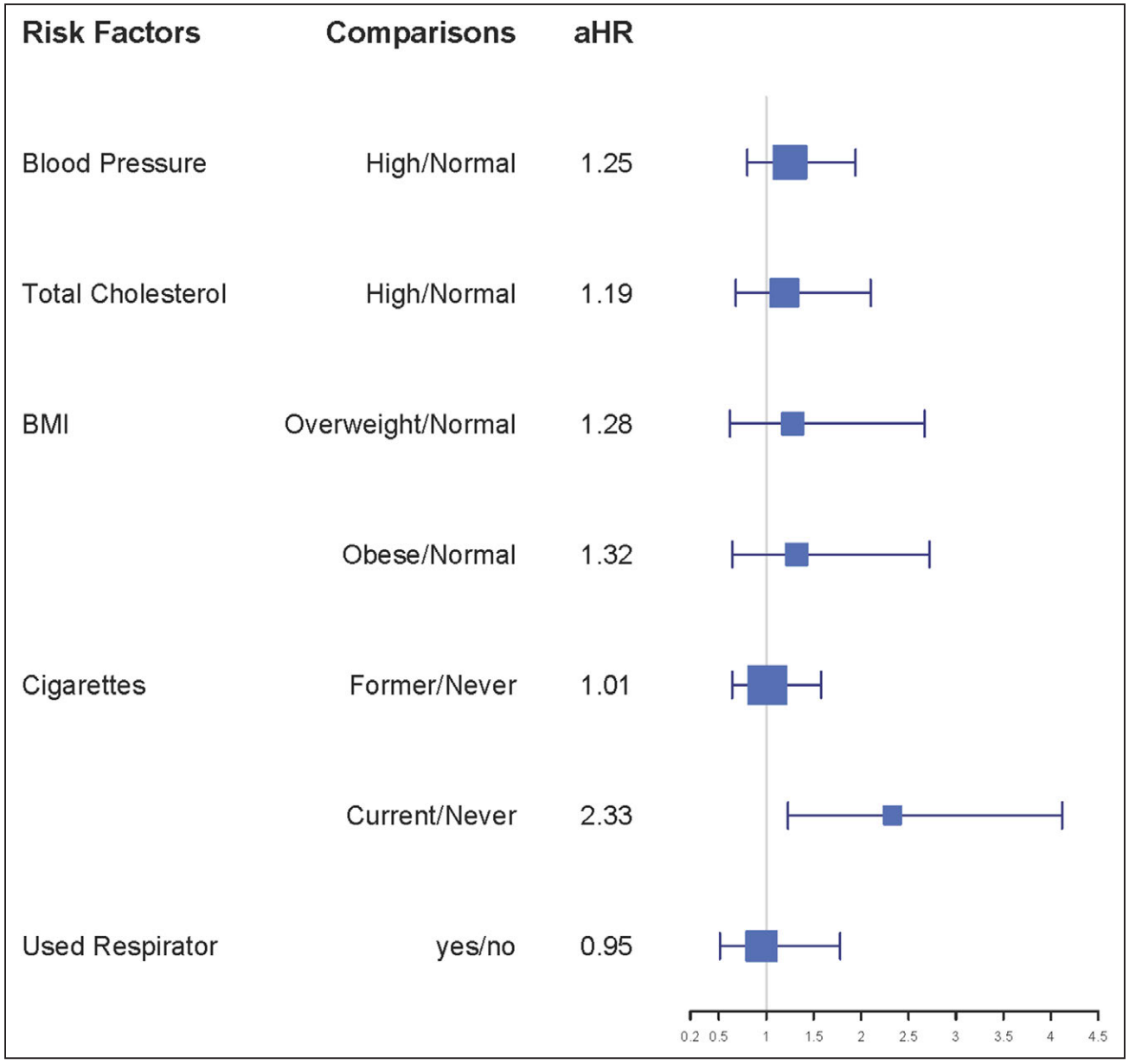

Figure 1. Adjusted* hazard ratios (aHRs) of pooled incident (including recurrent) myocardial infarctions and strokes and recognized risk factors in the World Trade Center–Heart cohort (n=5971)—New York, 2012 to 2016.

*Adjusted for use of a respirator and for recognized cardiovascular risk factors: age, blood pressure, total cholesterol, body mass index (BMI), tobacco use, and, when relevant, sex.

curves for MI or stroke by sex are shown in Figures I through IV in the Data Supplement.

Multivariable Analysis

In Figure 3 and Table VI in the Data Supplement the aHRs of PTSD were 2.22 (95% CI, 1.30–3.82) for 70 MIs, 2.51 (95% CI, 1.39–4.57) for 53 strokes, 2.35 (95% CI, 1.57–3.52) for 118 incident (including recurrent) pooled MI and stroke, and (not shown in a table or figure) 2.24 (95% CI, 1.39–3.63) for 83 incident (excluding recurrent) pooled MI and stroke. Five subjects had both MI and stroke. Specific results by sex and outcomes are provided in Table VI in the Data Supplement. In women, the estimated HRs for MI, stroke, and pooled MI and stroke were consistent with those observed among men.

Misclassification of Outcomes

Access to medical charts to validate the interview-based diagnosis was similar in cohort participants with (60%) and without PTSD (62%). The confirmation fraction was also similar across groups for stroke. However, for MIs, it was smaller for PTSD (47%) than for non-PTSD cases (74%). Such source of differential misclassifica-

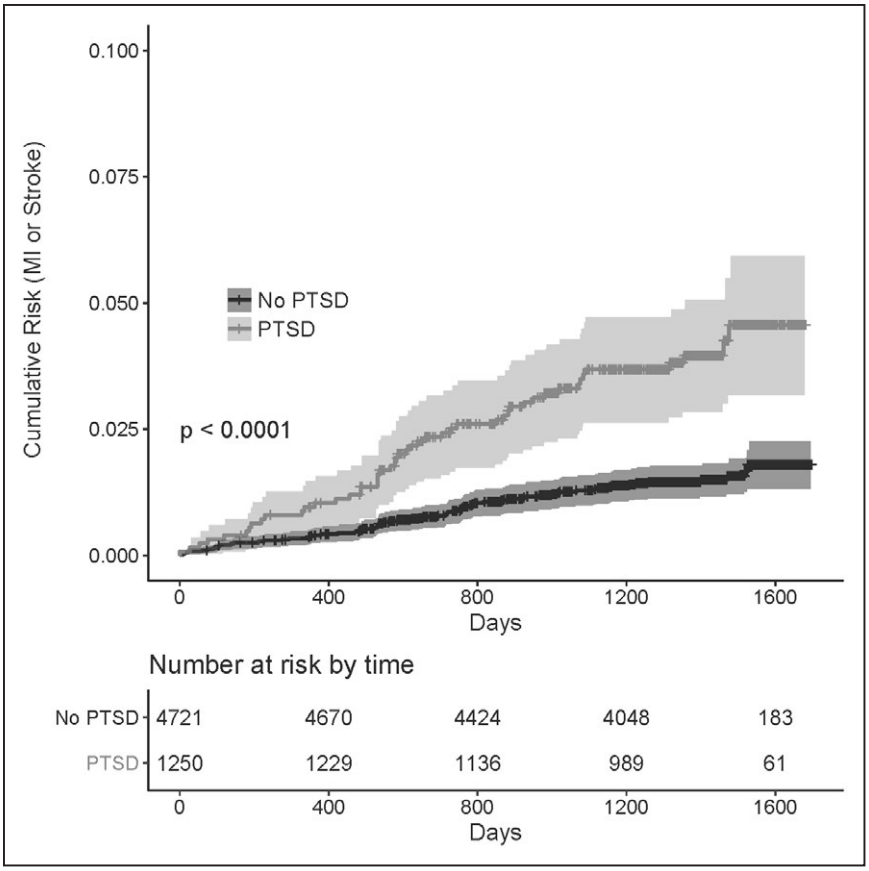

Figure 2. Cumulative risk of pooled incident (including recurrent) myocardial infarctions and strokes by post-traumatic stress disorder (PTSD) status in the World Trade Center-Heart cohort (n=5971)—New York, 2012 to 2016.
MI indicates myocardial infarction.

tion could spuriously strengthen the observed associations. We, therefore, repeated the analyses using discharge diagnoses for hospitalization in New York State for MI or stroke as outcomes—a measure independent of participant reports.

Hospitalization for MI or Stroke

These analyses were restricted to New York city or state residents (n=5484). All incident MI and strokes identified in interviews, whether confirmed or not in medical charts, were present in the SPARCS database. In contrast, 49 events (19 among subjects with PTSD and 30 among subjects without PTSD) were recorded in SPARCS but had been missed by the active follow-up. As shown in Figure 4 and Table VII in the Data Supplement for hospitalizations for MI or stroke in New York, aHRs were 2.17 (95% CI, 1.41–3.32) for 112 MIs, 3.01 (95% CI, 1.84–4.93) for 77 strokes, and 2.40 (95% CI, 1.73–3.34) for pooled 180. Nine subjects had been hospitalized for both MI and stroke. The association of PTSD and hospitalization for pooled MI and stroke adjusted for age only was statistically significant among women too (HR, 2.44; 95% CI, 1.05–5.55).

Of note, of the 415 lost to active follow-up, 228 (54.9%) had a record in SPARCS between January 2012 and December 2016. Of these 228, 4 had had an MI or a stroke, that is, 1.8% (95% CI, 0.0–3.5). This cumulative incidence of hospitalizations for MI or stroke in the lost to follow-up is of the same order of magnitude as that of 2.8% observed in the full cohort of (123/5971) during the same period.

Control of Depression

In the full cohort, there were 6 cases of MI or stroke in men with depression but no PTSD and 29 cases of MI or stroke in men with both depression and PTSD. Among men free of depression, the crude (not shown in the figures), age-adjusted, and multivariate (shown in Figures 3 and 4) HRs of MI or stroke were, respectively, 1.94 (95% CI, 1.07–3.50), 2.19 (95% CI, 1.21–3.95), and 1.88 (95% CI, 1.01–3.49) for incidence and 1.93 (95% CI, 1.19–3.02), 2.41 (95% CI, 1.49–3.75), and 2.27 (95% CI, 1.41–3.67) for hospitalization.

Mortality

There were 43 deaths identified in the cohort, of which 3 were from CVDs, 18 from other causes, and 22 from unknown causes.

PCL Score

When using the continuous PCL-C score instead of the dichotomized PTSD variable, the aHR of pooled MI or

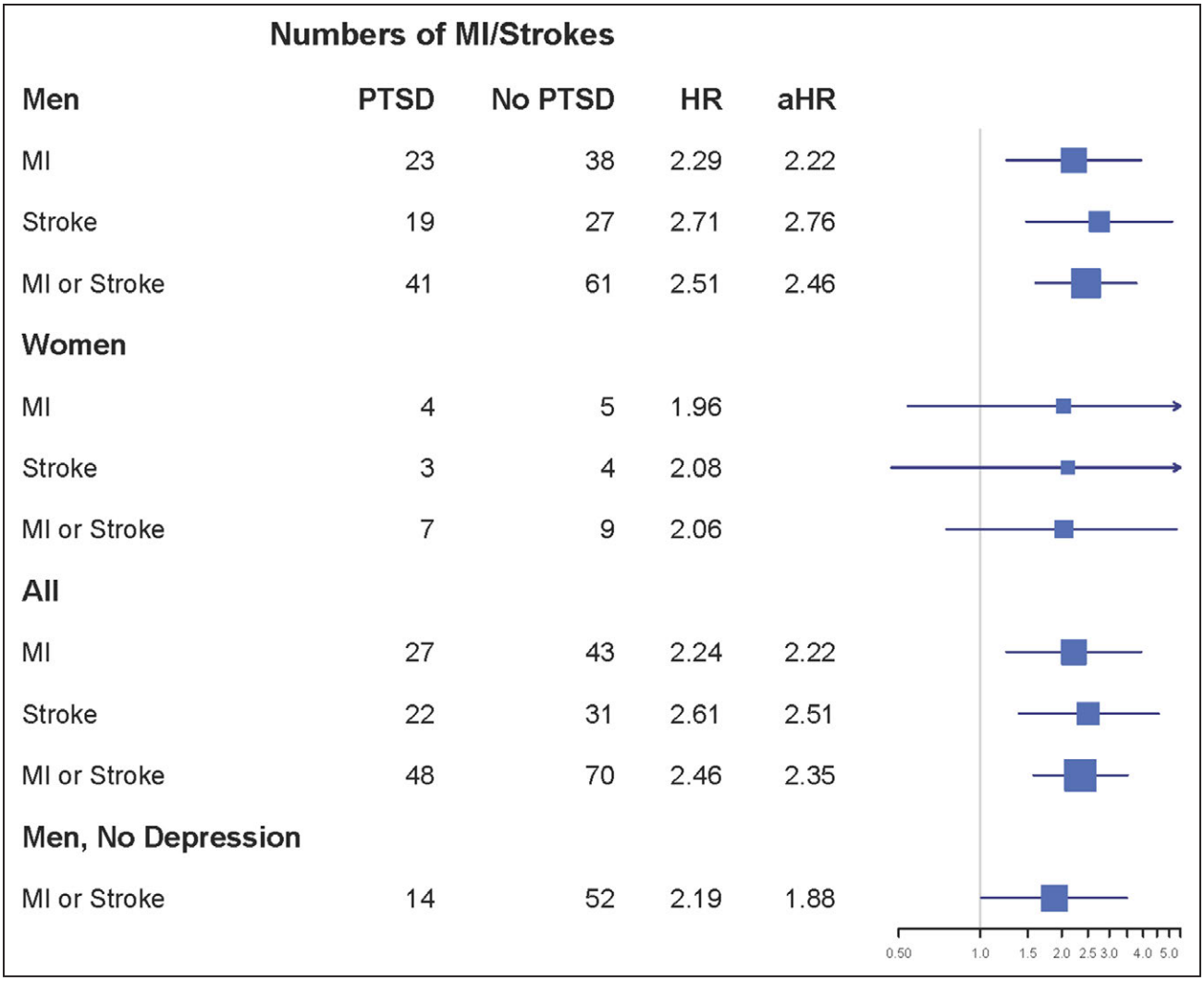

Figure 3. Age-adjusted hazard ratio (HR) and adjusted* HR (aHR) for post-traumatic stress disorder (PTSD) and pooled incident (including recurrent) myocardial infarctions and strokes in the World Trade Center–Heart cohort (n=5971)—New York, 2012 to 2016.
*Adjusted for use of a respirator and for recognized cardiovascular risk factors: age, blood pressure, total cholesterol, body mass index, tobacco use, and, when relevant, sex. MI indicates myocardial infarction.

stroke for each SD increase in PCL score was identical for both incident events and for hospitalizations: 1.58 (95% CI, 1.35–1.84) including recurrent cases and 1.36 (95% CI, 1.17–1.95) excluding recurrent cases.

DISCUSSION

After 4 years of active follow-up of WTC-Heart, PTSD comes out as a strong, independent determinant of MI and stroke, in both men and women, before and after controlling for recognized use of a respirator during cleanup of debris, cardiovascular risk factors, and depression. Hazard ratios were consistent when analyses were restricted to discharge diagnoses of MI and stroke derived from a New York hospital registry that did not include any patient self-reports.

Because of its methodological strength (ie, active follow-up, medical chart validation, and adjustment for depression), this study validates previous reports of exclusively male or female cohorts[4,5] and those of the WTC-Registry reports.[11,12] The independence of the PTSD and MI or stroke association from depression is consistent with most[4] but not all reports.[20,21]

PTSD and CVD in Women

The associations with PTSD were in the same order of magnitude for men and women, and, specifically, the association of PTSD and hospitalization for pooled MI and stroke was statistically significant in both sexes. Of the 3 previous cohort studies that examined women, 2 had only women,[7,10] and 1 lacked measured conventional cardiovascular risk factors.[11,12] The average ages of women at baseline in these 3 cohorts were 44.4,[7] 34,[10] and 32 years,[12] whereas women in WTC-Heart were 51.1 years of age at baseline. Thus, the present

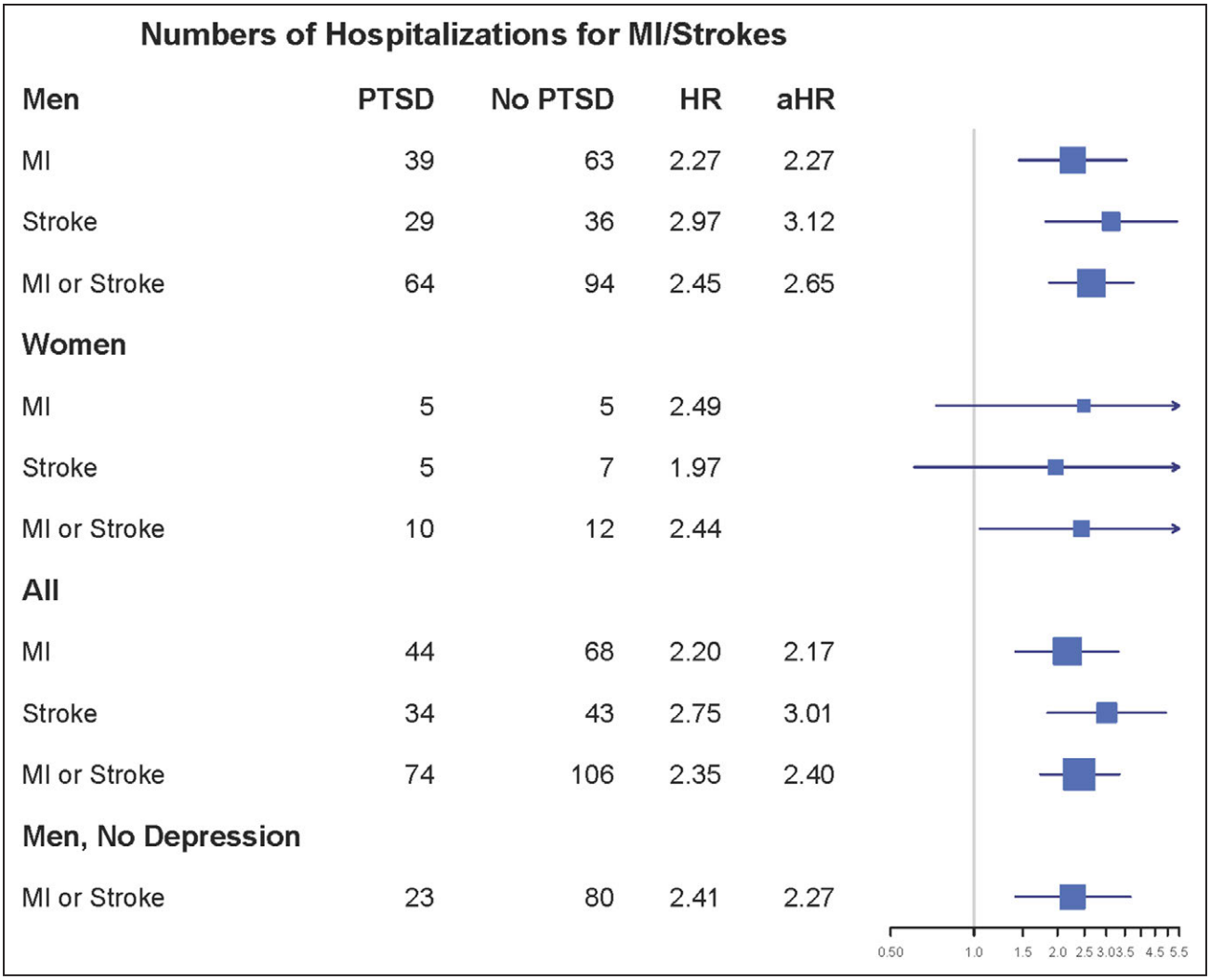

Figure 4. Age-adjusted hazard ratio (HR) and adjusted* HR (aHR) for post-traumatic stress disorder (PTSD) and hospitalizations for pooled (including recurrent) myocardial infarctions and strokes in the World Trade Center–Heart cohort (n=5484)—New York, 2012 to 2016.
*Adjusted for use of a respirator and for recognized cardiovascular risk factors: age, blood pressure, total cholesterol, body mass index, tobacco use, and, when relevant, sex. MI indicates myocardial infarction.

results add qualitatively to the evidence indicating that PTSD before menopause increases women's long-term risk of MI and stroke.[22]

Biological Plausibility

PTSD is a polythetic disorder consisting of clusters of symptoms potentially impacting cardiometabolic risk.[23,24] For example, PTSD may develop and persist because of fear manifested by nightmares, intense emotional and physiological re-experiencing of the trauma, active avoidance of cues or reminders of the trauma, and exaggerated startle response to threat.[25] Another cluster groups symptoms evoking major depression, such as anhedonia, detachment, restricted affect, sleep difficulty, and failing concentration.[26–28] In humans, the stress associated with these PTSD dimensions may upregulate amygdalar activity, activating both the sympathetic nervous system, releasing inflammatory cells from the bone marrow, and leading to atherosclerotic inflammation, MI, and stroke.[29–36] The similar effect sizes in this study suggest similar mechanisms relating PTSD and incident MI or stroke in men and women.[37]

Recognized Cardiovascular Risk Factors

Current smoking was the only recognized cardiovascular risk determinant in this cohort. Blood lipids, blood pressure, and body mass were not associated with MI or stroke. These recognized risk factors may play a role for individual cohort members, but they do not discriminate cardiovascular risk in this homogeneous cohort of blue-collar workers.

Because PTSD is more prevalent in this cohort (20.9%) than current smoking (7.1%) for aHRs of a similar magnitude of 2, ≈3× more cardiovascular cases are attributable to PTSD than to current smoking.

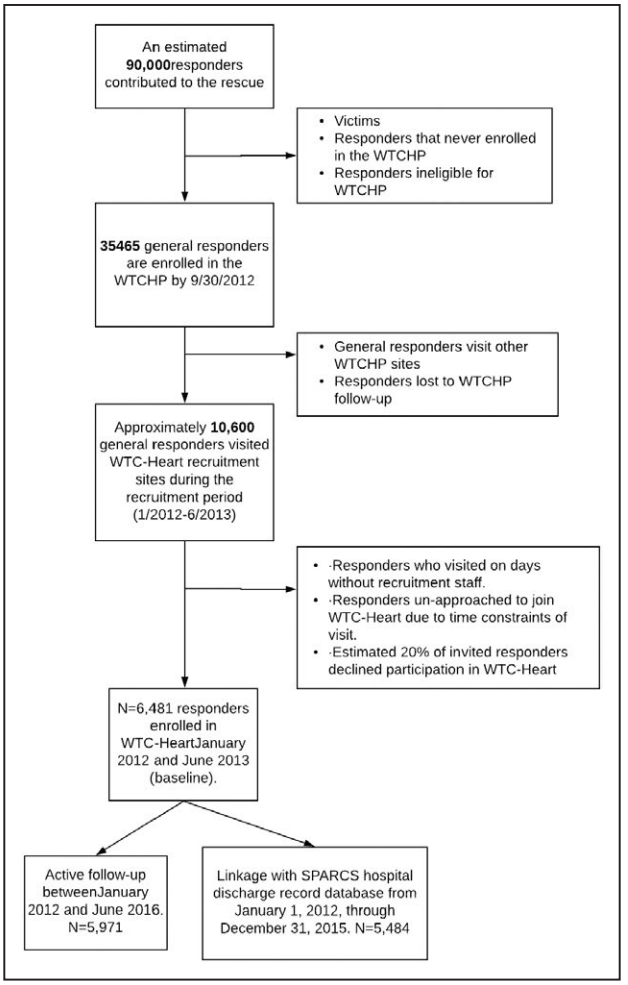

Figure 5. Flowchart and timeline of the World Trade Center (WTC) Health Program (WTCHP) and of WTC-Heart, 2001 to 2016.

Dust Exposure

None of the variables expressing exposure to the WTC dust, such as the timing and intensity of exposure to the dust cloud or the donning of a protective mask, were independently associated with subsequent MI or stroke in these analyses.

Limitations

The exposure severity and cardiovascular profile of the subcohort of survivors enrolled in the WTC-Heart subjects may not be representative of the estimated 90 000 individuals who originally responded to the September 11 disaster (Figure 5). However, given the homogeneity of the cohort of blue-collar worker in terms of cardiovascular risk, the selection process is unlikely to have biased the risk comparison among the enrollees between those who developed PTSD and those who did not. Moreover, the small losses to follow-up (7.9%) offer some protection against selection bias, in particular because we could establish that (1) the proportion of lost to follow-up was identical in men (7.9%) and women (7.7%), (2) the subjects lost to follow-up had a similar cardiovascular risk profile as those who remained in the cohort (Table VIII in the Data Supplement), and (3) the cumulative risk of MI and stroke for more than half of those who were never contacted after baseline but had a record in the New York State SPARCS program was of the same order of magnitude as the risk of the rest of the cohort.

We were not able to obtain the causes of death for 22 participants and do not know which proportion of the lost to follow-up died of CVDs. Incorporating cardiovascular deaths could have attenuated or exacerbated the present findings. However, the small number of cardiovascular deaths expected given the age distribution of the cohort is unlikely to have qualitatively modified the cumulative risks of events, which progressively diverged over time between participants with and without PTSD (Figure 2).

Also, because participants were sampled consecutively among subjects attending the WTCHP either for their annual visit or for health problems, we may have included people visiting the clinic more frequently because of poorer health problems than those only visiting the clinic once per year. However, as shown in Table I in the Data Supplement, the demographics of WTC-Heart were virtually identical to those of the whole WTCHP in which it was nested. Prevalences of PSTD in WTC-Heart were almost identical to those published for the whole WTCHP.[38]

Additional limitations include a self-report of PTSD based on the PCL-C questionnaire, residual confounding from self-report of depression based on the Patient Health Questionnaire-9 and recall of respirator use and exposure to the dust cloud, and the lack of assessment of potential biological mediators and unmeasured confounding (eg, prior trauma) of the association between PTSD and MI/stroke. However, similar baseline heart rate for those with and without PTSD suggests no specific factor that protects against both PTSD and MI/stroke.

Strengths

Because WTC-Heart is nested within the health program (ie, WTCHP) begun 1 year after the attack and currently providing lifetime free medical care for WTC-related medical conditions to first responders, the cohort study had a unique opportunity to recruit exposed workers 11 to 15 years after September 11 as they entered ages at which incidence of CVD increases rapidly and follow them up for 4 years with small losses (7.9%).

In agreement with previous WTC reports,[3] prevalence of PTSD in this cohort comprising a majority of nontrained responders was more than twice of that in the general population. This excess prevalence of PTSD provided statistical power to study the association of PTSD and cardiovascular outcomes in both sexes. The young age of the cohort participants, associated with

low rates of MI or stroke, negatively affected statistical power but allowed us to reasonably assume that few cases were missed during the 2001 to 2012 period. The young age may also have facilitated singling out the effect of PTSD for lack of competing causes.

In terms of validity and confounding controls, analyses were performed before and after adjustment for measured recognized cardiovascular risk factors; in men, the association was observed in the subgroup free of depression; interview-based outcomes were tentatively confirmed in medical charts; findings for interview-based diagnoses of incident MIs and stroke were reproduced after linkage to hospitalization records.

Conclusions

Because of its design, this cohort study offers unique and strong evidence that WTC attack–related PTSD is a risk factor for MI and stroke, in men and women, and independently of recognized cardiovascular risk factors and depression.

ARTICLE INFORMATION

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Correspondence

Alfredo Morabia, MD, PhD Department of Epidemiology, Mailman School of Public Health, Columbia University, W 168th St, New York, NY 10032. E-mail am52@cumc.columbia.edu

Affiliations

Barry Commoner Center for Health and the Environment, Queens College, City University of New York (M.R., Z.L., A.M.). University of North Carolina Gillings School Of Global Public Health, Chapel Hill (M.R.). University of Michigan School of Public Health, Epidemiology, Ann Arbor (Z.L.). James J. Peters Veterans Affairs Medical Center, Bronx, NY (J.F.). Department of Psychiatry, Icahn Mount Sinai School of Medicine, NY (J.F.). Department of Epidemiology, Mailman School of Public Health, Columbia University, NY (C.M.-M., A.M.).

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Disclosures

None.

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