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DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 88

[NIOSH Docket 094]

World Trade Center Health Program; Petition 018—Hypertension; Finding of Insufficient Evidence

AGENCY: Centers for Disease Control and Prevention, HHS.

ACTION: Denial of petition for addition of a health condition.

SUMMARY: On January 5, 2018, the Administrator of the World Trade Center (WTC) Health Program received a petition (Petition 018) to add hypertension (high blood pressure) to the List of WTC-Related Health Conditions (List). Upon reviewing the scientific and medical literature, including information provided by the petitioner, the Administrator has determined that the available evidence does not have the potential to provide a basis for a decision on whether to add hypertension to the List. The Administrator also finds that insufficient evidence exists to request a recommendation of the WTC Health Program Scientific/Technical Advisory Committee (STAC), to publish a proposed rule, or to publish a determination not to publish a proposed rule.

DATES: The Administrator of the WTC Health Program is denying this petition for the addition of a health condition as of [INSERT DATE OF PUBLICATION IN **FEDERAL REGISTER**].

FOR FURTHER INFORMATION CONTACT: Rachel Weiss, Program Analyst, 1090

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A. WTC Health Program Statutory Authority

Title I of the James Zadroga 9/11 Health and Compensation Act of 2010 (Pub. L. 111-347, as amended by Pub. L. 114-113), added Title XXXIII to the Public Health Service (PHS) Act,¹ establishing the WTC Health Program within the Department of Health and Human Services (HHS). The WTC Health Program provides medical monitoring and treatment benefits to eligible firefighters and related personnel, law enforcement officers, and rescue, recovery, and cleanup workers who responded to the September 11, 2001, terrorist attacks in New York City, at the Pentagon, and in Shanksville, Pennsylvania (responders), and to eligible persons who were present in the dust or dust cloud on September 11, 2001, or who worked, resided, or attended school, childcare, or adult daycare in the New York City disaster area (survivors).

All references to the Administrator of the WTC Health Program (Administrator) in this notice mean the Director of the National Institute for Occupational Safety and Health (NIOSH) or his designee.

¹ Title XXXIII of the PHS Act is codified at 42 U.S.C. 300mm to 300mm-61. Those portions of the James Zadroga 9/11 Health and Compensation Act of 2010 found in Titles II and III of Public Law 111-347 do not pertain to the WTC Health Program and are codified elsewhere.

Pursuant to section 3312(a)(6)(B) of the PHS Act, interested parties may petition the Administrator to add a health condition to the List in 42 CFR 88.15. Within 90 days after receipt of a valid petition to add a condition to the List, the Administrator must take one of the following four actions described in section 3312(a)(6)(B) of the PHS Act and § 88.16(a)(2) of the Program regulations: (1) Request a recommendation of the STAC; (2) publish a proposed rule in the *Federal Register* to add such health condition; (3) publish in the *Federal Register* the Administrator's determination not to publish such a proposed rule and the basis for such determination; or (4) publish in the *Federal Register* a determination that insufficient evidence exists to take action under (1) through (3) above.

B. Procedures for Evaluating a Petition

In addition to the regulatory provisions, the WTC Health Program has developed policies to guide the review of submissions and petitions,² as well as the analysis of evidence supporting the potential addition of a non-cancer health condition to the List.³

A valid petition must include sufficient medical basis for the association between the September 11, 2001, terrorist attacks and the health condition to be added; in accordance with WTC Health Program policy, 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 may demonstrate the required medical basis.⁴ Studies linking 9/11 agents to the petitioned health condition may also provide sufficient medical basis for a valid petition.

After the Program has determined that a petition is valid, the Administrator must direct the Program to conduct a review of the scientific literature to determine if the available scientific

² See WTC Health Program [2014], *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions*, May 14, 2014, <http://www.cdc.gov/wtc/pdfs/WTCHPPPpetitionHandlingProcedures14May2014.pdf>.

³ See WTC Health Program [2017], *Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions*, February 14, 2017, https://www.cdc.gov/wtc/pdfs/WTCHP_PP_Adding_NonCancers_14_February_2017.pdf.

⁴ See *supra* note 2.

information has the potential to provide a basis for a decision on whether to add the health condition to the List.⁵ The literature review includes a search for peer-reviewed, published, epidemiologic studies (including direct observational studies in the case of health conditions such as injuries) about the health condition among 9/11-exposed populations. The Program evaluates the scientific quality limitations of each peer-reviewed, published, epidemiologic study of the health condition identified in the literature search; the Program then compiles the scientific results of each study to assess whether a causal relationship between 9/11 exposures and the health condition is supported, and evaluates whether the results of the studies are representative of the 9/11-exposed population of responders and survivors. A health condition may be added to the List if peer-reviewed, published, epidemiologic studies provide support that the health condition is substantially likely⁶ to be causally associated with 9/11 exposures. If the evaluation of evidence provided in peer-reviewed, published, epidemiologic studies of the health condition in 9/11 populations demonstrates a high, but not substantial, likelihood of a causal association between the 9/11 exposures and the health condition, then the Administrator may consider additional highly relevant scientific evidence regarding exposures to 9/11 agents⁷ from sources using non-9/11-exposed populations. If that additional assessment establishes that the health condition is substantially likely to be causally associated with 9/11 exposures among 9/11-exposed populations, the health condition may be added to the List.

C. Petition 018

On January 5, 2018, the Administrator received a petition (Petition 018) from a WTC responder who worked at Ground Zero, requesting the addition of “hypertension -- high blood

⁵ See *supra* note 3.

⁶ The “substantially likely” standard is met when the scientific evidence, taken as a whole, demonstrates a strong relationship between the 9/11 exposures and the health condition.

⁷ 9/11 agents are chemical, physical, biological, or other agents or hazards reported in a published, peer-reviewed exposure assessment study of responders or survivors who were present in the New York City disaster area, at the Pentagon site, or at the Shanksville, Pennsylvania site, as those locations are defined in 42 CFR 88.1.

pressure” to the List.⁸ The petition included one scientific article reviewing the findings of peer-reviewed, published epidemiologic studies concerning the association of hypertension and cardiovascular disease with post-traumatic stress disorder (PTSD), by McFarlane [2010].⁹ The McFarlane article on its own did not provide a medical basis, but it did provide a reference to a peer-reviewed, published study by Gerin *et al.* [2005]¹⁰ of hypertension in populations that were potentially affected by the September 11, 2001, terrorist attacks, in New York City, Washington D.C., Chicago, and Mississippi, suggesting an association between 9/11 exposures and the health condition. The inclusion of a reference to this study in the submission provides sufficient medical basis for the submission to be considered a valid petition.

D. Review of Scientific and Medical Information and Administrator Determination

In response to Petition 018, and pursuant to the Program policy on the addition of non-cancer health conditions to the List,¹¹ the Program conducted reviews of the scientific literature on hypertension.¹² Through the literature search, the Program identified 21 references to review for relevance;¹³ of those identified references, three were found to be relevant peer-reviewed, published, epidemiologic studies of hypertension in 9/11-exposed populations: Simeon *et al.* [2008],¹⁴ Trasande *et al.* [2013],¹⁵ and Kim *et al.* [2018].¹⁶ At this stage of the evaluation process,

⁸ See Petition 018, WTC Health Program: Petitions Received, <http://www.cdc.gov/wtc/received.html>.

⁹ McFarlane AC [2010], *The Long-Term Costs of Traumatic Stress: Intertwined Physical and Psychological Consequences*, World Psychiatry 9:3-10.

¹⁰ Gerin W, Chaplin W, Schwartz JE, *et al.* [2005], *Sustained Blood Pressure Increase After an Acute Stressor: the Effects of the 11 September 2001 Attack on the New York City World Trade Center*, Journal of Hypertension 23(2):279-284.

¹¹ *Supra* note 3.

¹² Databases searched include: NIOSHTIC-2, ProQuest Health & Safety, PubMed, Scopus, Toxicology Abstracts/TOXLINE, and Medline.

¹³ The 21 studies included a study by Jordan *et al.* [2011], which the Program evaluated and determined not to be relevant to an evaluation of hypertension among the 9/11 population. The study’s authors evaluated cardiovascular disease hospitalizations among WTC Health Registry members; however, hypertension was grouped with other cardiovascular conditions and, therefore, the effect of 9/11 exposures on hypertension hospitalizations could not be ascertained. Jordan HT, Brackbill RM, Cone JE, *et al.* [2011], *Mortality among survivors of the Sept 11, 2001, World Trade Center disaster: results from the World Trade Center Health Registry cohort*, Lancet 378(9794):879-887.

¹⁴ Simeon D, Yehuda R, Knutelska M, *et al.* [2008], *Dissociation versus posttraumatic stress: cortisol and physiological correlates in adults highly exposed to the World Trade Center attack on 9/11*, Psychiatry Research 161(3):325-329.

¹⁵ Trasande L, Fiorino EK, Attina T, *et al.* [2013], *Associations of World Trade Center exposures with pulmonary and cardiometabolic outcomes among children seeking care for health concerns*, The Science of the Total Environment 444:320-326.

¹⁶ Kim H, Kriebel D, Liu B, *et al.* [2018], *Standardized morbidity ratios of four chronic health conditions among World Trade Center responders: Comparison to the National Health Interview Survey*, American Journal of Industrial Medicine (accepted for publication).

the Gerin *et al.* [2005] study was more carefully reviewed. The study population in Gerin *et al.* [2005] included participants residing in New York City and Washington D.C. who might have been exposed to reports of the September 11, 2001, terrorist attacks, in “newspapers, radio and television broadcasts, magazine articles, and web-based discussions, literally every day from the time they occurred...”¹⁷ None of the participants were reported to have been first responders, volunteers, or survivors of the terrorist attacks, or to have been directly exposed to 9/11 agents. Accordingly, the Administrator determined that Gerin *et al.* [2005] is not an epidemiologic study of hypertension in the 9/11-exposed populations and does not meet the threshold for relevance established in the Program policy; therefore, the study is not further reviewed below.

Simeon *et al.* [2008]. The cross-sectional study¹⁸ by Simeon *et al.* [2008] was designed to “investigate perturbations in the major stress response systems . . . after the 9/11 attack, with a specific focus of dissecting unique correlates of posttraumatic stress versus dissociative symptomatology.” The authors’ primary hypothesis was that dissociation and posttraumatic stress show different associations to cortisol and psychophysiological measures (dexamethasone suppression, psychosocial stress reactivity, and physiological stress reactivity). Blood pressure and heart rate were also measured to allow comparisons between physiologic measures of dissociation and posttraumatic stress in exposed and unexposed study participants. Participants included 21 New York City residents considered “highly exposed to 9/11,” as well as 10 New York City residents who did not have significant 9/11 exposure or a diagnosis of posttraumatic stress disorder (PTSD), who served as the control group. Exposed participants reported being inside a tower, being in very close proximity to Ground Zero, losing a close loved-one, or participating in rescue and recovery efforts. Mean resting systolic blood pressure, mean resting diastolic blood pressure, mean peak Trier Social Stress Test (TSST) systolic blood pressure, and

¹⁷ *Supra* note 10, at 283.

¹⁸ An observational study that analyzes data from a population or sub-set of a population at a specific point in time.

mean peak TSST diastolic blood pressure¹⁹ did not differ significantly between the exposed and unexposed groups, even among seven of the 21 exposed participants who met criteria for a diagnosis of PTSD.

The Program found several limitations with the Simeon *et al.* [2008] study. First, the study inadequately adjusted for confounding; because the authors did not provide enough information about the control group, the Program was unable to determine whether adjustments had been made for all potential confounders. Second, the study inadequately addressed recruitment bias; the exposed study participants were recruited by newspaper advertisement, which primarily captures those individuals who subscribe to or purchase the newspaper and thus may not be representative of the entire 9/11-exposed population. Third, the study incompletely considered all aspects of exposure; the authors described the experimental and control groups only as “highly exposed” and no “significant exposure,” respectively, rather than seeking to quantitatively or qualitatively characterize the different types of exposure experienced by participants, as well as the intensity and duration of their exposures, and the resulting impacts on health outcomes. Finally, the study insufficiently addressed the inadequacies of the referent population; the study employs a small sample size and thus lacks adequate power to evaluate the association between 9/11 exposure and hypertension.

Trasande *et al.* [2013]. The second study, by Trasande *et al.* [2013], is also a cross-sectional study. It was designed to examine the impact of clinically-reported exposures on the health of children who were exposed to the terrorist attack in New York City. Study participants included 148 patients who were 18 years of age or younger on September 11, 2001, enrolled in the WTC Environmental Health Center (the health program for 9/11 survivors that predated the WTC Health Program). The authors compared blood pressure data from the study population²⁰

¹⁹ Blood pressure was measured at rest (averaged over four hourly time points) and at its peak during TSST. The study did not provide any information about equipment used or guidelines followed to measure blood pressure.

²⁰ Blood pressure was measured using a Philips SureSigns VS3 oscillometric sphygmomanometer with appropriate cuff size for arm length, following American Heart Association guidelines in Urbina E, Alpert B, Flynn J, Hayman L, Harshfield GA, Jacobson M, *et*

with that of children 6 to 19 years of age, reported in CDC's National Health and Nutrition Examination Survey (NHANES) 2001-2006. The authors developed exposure categories for dust cloud exposure and presence/absence at their home residence one day during September 11-18, 2001, but none were used in the evaluation of an association with prehypertension or hypertension. The study found that 45.5 percent of children in the study population were prehypertensive and 10.6 percent were hypertensive, compared with the NHANES data, in which 6.9 percent were prehypertensive and 2.4 percent were hypertensive;²¹ prehypertension among the study group was positively associated with older age (+9.5% odds/year older, p=0.024).

Although the results of Trasande *et al.* [2013] suggest possible cardiovascular effects, the Program found several major limitations with the study. First, the study inadequately adjusted for possible confounders; although the authors identify that an important confounder is living in an urban setting where the types and concentrations of particulates are different than in other settings, no adjustments were made to account for the setting, limiting the value of the comparing the urban study population's blood pressure data with NHANES data, which includes data from suburban and rural populations likely exposed to different types and concentrations of particulates. Second, the study inadequately addressed recruitment bias; the authors selected participants from among those who presented to the WTC Environmental Health Center, and were ≤ 18 years old on September 11, 2001 and thus may have been sicker than the general population of survivors. Third, the study incompletely considered all aspects of exposure; 9/11 exposure among participants with hypertension was not considered or evaluated. Finally, the study insufficiently addressed the inadequacies of the referent population; the study does not describe whether the NHANES sample has a comparable ethnic composition and residential

al. [2008], *Ambulatory blood pressure monitoring in children and adolescents: recommendations for standard assessment: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the council on cardiovascular disease in the young and the council for high blood pressure research*, *Hypertension* 52:433-51. The guidelines referenced by the study authors are for ambulatory blood pressure monitoring, not single clinic measurements as were conducted during the study.

²¹ The study authors categorized blood pressure (BP) outcomes as follows: present/absent prehypertension (BP $\geq 90^{\text{th}}$ percentile for age/height Z-score/gender or systolic BP ≥ 120 mm Hg or diastolic BP ≥ 80 mm Hg) and present/absent hypertension (BP $\geq 95^{\text{th}}$ percentile for age/height Z-score/gender or systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg).

setting to that of the study group. Although the study did find a relatively high frequency of cardiometabolic risks, including elevated blood pressure, the authors did not evaluate the association between 9/11 exposure and hypertension.

Kim *et al.* [2018]. The third study, a prospective cohort study²² by Kim *et al.* [2018], was designed to compare the lifetime prevalence of hypertension, asthma, diabetes, and cancer among WTC responders currently enrolled in the WTC Health Program, with a referent group from the National Health Interview Survey (NHIS). Hypertension²³ among WTC responders was self-reported, as was exposure to WTC dust and other stressors. After comparing annual standardized morbidity ratios for hypertension prevalence, the authors found that hypertension prevalence was statistically significantly increased among male WTC responders between 2007 and 2009, peaking at 1.17 (95% CI 1.13-1.22) in 2008, but decreased among male WTC responders in 2010, which was the last year studied. Hypertension prevalence was never elevated among women. The authors ultimately concluded that the slightly higher prevalence of hypertension in men in the study group may be associated with WTC-related PTSD and that further analysis and follow-up of WTC responders is warranted.

The Program identified several limitations with the Kim *et al.* [2018] study. First, the study inadequately adjusted for confounders; the standardized morbidity ratios were age-adjusted, but not adjusted for other confounders. Second, the study did not adequately adjust for recruitment bias; the authors acknowledge that selection bias is likely because sicker WTC responders may have been more likely to enroll in the WTC Health Program and attend follow-up examinations more frequently. Third, the study incompletely considered all aspects of exposure; the authors described the WTC responder and referent groups only as “exposed” and “unexposed,” respectively. Fourth, the study incompletely addressed the inadequacies of the

²² A study that follows a cohort of similar individuals over time to determine how risk factors affect health outcomes.

²³ Responders who participated in the Kim *et al.* [2018], study were asked: “Has a doctor ever told you that you had high blood pressure?” The Program assumes the authors define hypertension as having responded “yes” to this questions, although this level of detail was not provided by the authors. Participants of the NHIS study were asked: “Have you ever been told by a doctor or health professional that you have hypertension, also called high blood pressure?” Kim *et al.* [2018] provides no further information provided regarding the study’s definition of “high blood pressure” or “hypertension.”

referent population; the NHIS data, while representative of the U.S. population, is likely not comparable to the WTC responder cohort. Finally, outcome data in the study was incomplete; the authors used self-reported hypertension rather than conducting blood pressure measurements in study participants, and used different questions to define hypertension in the WTC responder group compared with the referent group.

Together, all three studies were assessed to determine whether a causal relationship between 9/11 exposures and hypertension is supported. The Program uses the following Bradford Hill criteria to evaluate studies of 9/11-exposed populations: strength of association, precision of the risk estimate, consistency of findings, biological gradient, and plausibility and coherence. Only one of the three studies demonstrated a statistically significant increase in hypertension among WTC responders (Kim *et al.* [2018]); one study found no statistically significant differences in blood pressure between exposed and unexposed participants (Simeon *et al.* [2008]); and one study used an inadequate comparison group and this faulty study design feature precluded an evaluation of the association between 9/11 exposures and the risk of hypertension (Trasande *et al.* [2013]). Only one of the three studies demonstrated a precise risk estimate (Kim *et al.* [2018]); risk estimates were not calculated in the other two studies. The studies did not share a single definition of hypertension, and, ultimately, their findings were not consistent, as only Kim *et al.* [2018] showed a statistically significant increase in hypertension among WTC responders. The biological gradient and dose response were not evaluated in any of the studies. Although none of the studies evaluated a causal association between hypertension and WTC dust, the Program finds it plausible and coherent that 9/11 exposures may increase blood pressure, possibly through one or more of the following mechanisms: (1) systemic oxidative stress/inflammation, (2) elevated endothelin levels or activity, or (3) altered autonomic nervous

system balance,²⁴ and this is consistent with the results presented by Trasande *et al.* [2013] and Kim *et al.* [2018].

Finally, the three studies were reviewed to determine whether the studies represent both the WTC responder and survivor populations or a subgroup of those populations, or whether the results can be extrapolated to the entire 9/11-exposed population. The Program found that only one study demonstrated that the results could be extrapolated to the population of WTC responders (Kim *et al.* [2018]); another study was conducted among a potentially non-representative and small sample of WTC survivors (Simeon *et al.* [2008]), and the final study did not describe a sampling procedure to allow an assessment of representativeness (Trasande *et al.* [2013]).

The studies described and evaluated above had limitations and lacked consistency among their results. Neither the one study that showed a statistically significant increase in hypertension among WTC responders, Kim *et al.* [2018], nor all three studies, taken together, were able to demonstrate that hypertension is substantially likely to be causally associated with 9/11 exposures among 9/11-exposed populations.

E. Administrator's Final Decision on Whether to Propose the Addition of Hypertension to the List

The Administrator has determined that insufficient evidence is available to take further action at this time, including proposing the addition of hypertension to the List (pursuant to PHS Act, sec. 3312(a)(6)(B)(ii) and 42 CFR 88.16(a)(2)(ii)) or publishing a determination not to publish a proposed rule in the *Federal Register* (pursuant to PHS Act, sec. 3312(a)(6)(B)(iii) and 42 CFR 88.16(a)(2)(iii)). The Administrator has also determined that requesting a

²⁴ See Brook RD, Urch B, Dvonch JT, *et al.* [2009], *Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans*, *Hypertension* 54(3):659-667.

recommendation from the STAC (pursuant to PHS Act, sec. 3312(a)(6)(B)(i) and 42 CFR 88.16(a)(2)(i)) is unwarranted.

For the reasons discussed above, the Petition 018 request to add hypertension to the List of WTC-Related Health Conditions is denied.

The WTC Health Program may consider hypertension to be a condition medically associated with a certified WTC-related health condition in individual cases. Program members who think their hypertension is a progression or side effect of treatment of a certified WTC-related health condition should ask their WTC Health Program medical provider whether their hypertension might be considered a medically associated health condition.

F. Approval to Submit Document to the Office of the Federal Register

The Secretary, HHS, or his designee, the Director, Centers for Disease Control and Prevention (CDC) and Administrator, Agency for Toxic Substances and Disease Registry (ATSDR), authorized the undersigned, the Administrator of the WTC Health Program, to sign and submit the document to the Office of the Federal Register for publication as an official document of the WTC Health Program. Robert Redfield M.D., Director, CDC, and Administrator, ATSDR, approved this document for publication on April 18, 2018.

John J. Howard,
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Department of Health and Human Services.

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