

# Herbicide Exposure, Vietnam Service, and Hypertension Risk in Army Chemical Corps Veterans

Yasmin S. Cypel, PhD, MS, Amii M. Kress, PhD, MPH, Stephanie M. Eber, MPH,  
Aaron I. Schneiderman, PhD, MPH, and Victoria J. Davey, PhD, MPH

**Objective:** We examined hypertension risk in Army Chemical Corps (ACC) veterans who sprayed defoliant in Vietnam. **Methods:** We analyzed data from the 2013 health survey of 3086 ACC veterans and investigated the association between self-reported physician-diagnosed-hypertension (SRH) and herbicide-spray-history adjusting for Vietnam-service-status, rank, age, tobacco/alcohol use, race, and body mass index (BMI). Spray-history was verified against serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) ( $n = 636$ ). SRH was confirmed by blood pressure (BP) measurement by trained medical technicians and medical record reviews. **Results:** Herbicide-spray-history (OR<sub>adjusted</sub>[95%confidence interval {CI}] = 1.74[1.44,2.11]) and Vietnam-service-status (OR<sub>adjusted</sub> = 1.26[1.05,1.53]) were significantly associated with SRH. The association was highest when comparing Vietnam-service-sprayers to non-Vietnam-service-nonsprayers (OR<sub>adjusted</sub> = 2.21[1.76,2.77]). Serum TCDD was highest for Vietnam-service-sprayers. Mean systolic BPs were significantly higher among veterans with SRH than those without ( $P \leq 0.001$ ). Medical records and SRH overall agreement was 89%. **Conclusion:** Occupational herbicide exposure history and Vietnam-service-status were significantly associated with hypertension risk.

At the height of American involvement in the Vietnam War in 1969,<sup>1</sup> approximately one in 10 US men aged 18 to 44 served in the military.<sup>2,3</sup> Now 40 years since the last US troops left Vietnam, there are an estimated 2.3 to 3.5 million surviving veterans who served there.<sup>1,4</sup> Vietnam veterans comprise 22% to 33% of US men aged 65 to 75.<sup>5</sup> Vietnam War veterans have lived with physical, toxicological, and psychological consequences of their wartime service, but no chemical has generated as much concern for long-term health as that of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), a contaminant of the 2,4,5-trichlorophenoxyacetic acid component of the herbicide “Agent Orange” (AO). Although TCDD is just one of many polychlorinated dibenzodioxins (PCDDs) that ubiquitously exist, 2,3,7,8-TCDD is still commonly referred to as dioxin (hereinafter, dioxin, or TCDD).

AO was the predominant herbicide sprayed between 1965 and 1970<sup>1,6</sup> and was sprayed mainly in South Vietnam Military Region III<sup>1</sup> where much of the ground combat occurred. A key emerging health outcome that may be related to TCDD exposure is hypertension. The biological mechanism for dioxin’s impact on hypertension is being investigated in animal models and humans but

proposed actions to date include adverse effects on gene expression,<sup>7</sup> vascular function,<sup>8</sup> and lipid and glucose metabolism.<sup>9</sup>

Between approximately 1965 and 1973, there were 22 US Army units assigned to do chemical operations in Vietnam.<sup>10</sup> These units made up what was known as the “US Army Chemical Corps (ACC)” in Vietnam. Using hand-mounted equipment and H-34-type helicopters, the men in these units sprayed herbicides around Special Forces camps, airfields, depots, and other facilities to defoliate areas immediately surrounding these sites and to destroy enemy food supplies through small-scale crop destruction.<sup>1,10,11</sup> Their chemical applications ranged from the use of three gallon capacity back-pack-type, hand-spray dispensers to the management of 200 gallon capacity helicopter spray systems used for spraying large areas.<sup>11,12</sup> In addition, the ACC was responsible for the storage, handling, mixing, and application of other chemicals (riot control agents [tear gas], and burning agents [napalm]), as well as the cleaning and maintenance of spray and storage equipment.<sup>10,13</sup> Overall, the ACC was responsible for approximately 4% to 5% of the herbicides applied in South Vietnam.<sup>13</sup>

There are past studies of Vietnam War veterans who were directly involved in chemical operations that investigated the relationship among hypertension, service in Vietnam, and/or herbicide exposure. In a 1999 to 2000 study<sup>14</sup> of ACC veterans, there was a significant association between self-reported hypertension (OR<sub>adjusted</sub>[95% confidence interval {CI}] = 1.32, [1.08,1.61]) and spraying herbicides in Vietnam. Of the three ACC veteran mortality studies, none reported significant excess mortality risk due to circulatory disease or hypertension for veterans who served in Vietnam (Vietnam veterans) relative to veterans of the Vietnam War era who never served in Southeast Asia (non-Vietnam veterans)<sup>15,16</sup> or to men in the US population.<sup>10,15,16</sup> For most of these studies numbers of decedents at the time of the study were small, reflecting the relatively young age of these veterans. For enlisted Air Force Ranch Hand (AFRH) ground personnel who handled herbicides during the War and had the highest serum dioxin levels, significantly increased circulatory disease mortality risk (standardized mortality ratio = 1.5 [1.0,2.2]) was found when compared to unexposed Air Force veterans<sup>17</sup> but hypertensive disease could not be assessed due to low numbers and no adjustment was made for smoking or family history. Later follow-up in enlisted ground personnel showed similar significant (relative risk = 1.7 [1.2 to 2.4];  $P = 0.001$ ) findings for circulatory disease while results for hypertension were not.<sup>18</sup>

Relative to studies of ACC and AFRH personnel who were highly exposed to chemicals, some studies of Vietnam War veterans with presumably less chemical exposure indicate that hypertension prevalence was greater for those who served in Vietnam relative to non-Vietnam veterans<sup>19</sup> or to the general population.<sup>20</sup> Yet, the Centers for Disease Control and Prevention’s (CDC) Vietnam Experience Study (VES) found no significant difference (OR = 1.1 [0.9,1.2]) between US men who served in Vietnam and non-Vietnam veterans for hypertension or other cardiorespiratory conditions determined through medical examinations.<sup>21</sup> Similarly, for over 180,000 Korean Vietnam veterans, no relationship was found between hypertension mortality and AO exposure level (hazard ratio = 1.18 [0.88,1.58];  $P = 0.28$ ).<sup>22</sup> No significant

From the Epidemiology Program, Post-Deployment Health Services (10P4Q), Office of Patient Care Services, Department of Veterans Affairs, Washington, DC (Dr Cypel, Dr Kress, Ms Eber, Dr Schneiderman); and Office of Research and Development, Veterans Health Administration, Washington, DC (Dr Davey).

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Address correspondence to: Yasmin S. Cypel, PhD, MS, Department of Veterans Affairs, Epidemiology Program, Post-Deployment Health Services (10P4Q), Office of Patient Care Services, 810 Vermont Avenue NW, Washington DC 20420 (yasmin.cypel@va.gov).

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association was also found ( $OR_{adjusted} = 1.00 [0.97, 1.02]$ ) between hypertensive disease reported to the Korean National Health Insurance claim database and AO exposure.<sup>23</sup> TCDD-exposed Korean Vietnam War veterans showed significantly greater ( $P = 0.04$ ) prevalence of hypertension (71.1%) than unexposed veterans (60%) but this study was limited to coronary patients.<sup>24</sup>

The relationship between TCDD and cardiovascular outcomes has also been studied in nonmilitary populations. Hypertension mortality was greatest for individuals who resided in highly TCDD contaminated areas in Seveso, Italy relative to those who resided in less exposed areas.<sup>25,26</sup> However, no association between serum TCDD and cardiovascular outcomes was found in studies of highly exposed US chemical workers conducted by the National Institute for Occupational Safety and Health, CDC.<sup>27,28</sup>

In addition, studies of residents of other areas compromised by chemical accidents or of general populations in the US and other countries showed associations of hypertension,<sup>29–35</sup> cardiovascular disease,<sup>36</sup> and metabolic syndrome<sup>31,35,37</sup> with other organic pollutant exposure (POP) (eg, polychlorinated dibenzofurans, polychlorinated biphenyls [PCBs], or organochlorine pesticides). But, a study of Greenland Inuit who have extremely high serum POP levels reported no significant association between blood pressure and PCBs or organochlorine pesticides.<sup>38</sup> There is no evidence indicating that veterans of the Vietnam War were exposed to substantial amounts of other types of polychlorinated hydrocarbons.<sup>9</sup>

The quantification of past herbicide exposure in Vietnam is difficult because of the lack of chemical measurement in the environment at the time of spraying, consistency and availability of military records that establish ground troop or unit location in Vietnam, and knowledge about the defoliant's environmental fate and bioavailability. Consequently, surrogate or proxy methods have been used to assess herbicide exposure like self-reported or perceived exposure data,<sup>14,19,39–41</sup> military occupation,<sup>42</sup> and geographic-based models developed from military records and aerial herbicide spray mission data.<sup>19,22,23,39–41,43</sup>

Blood serum TCDD levels<sup>14,40,44–48</sup> have been used in studies of US and Korean Vietnam War veterans and the Vietnamese populace<sup>49</sup> to assess the likelihood of individuals' past exposure to herbicides, namely AO. TCDD levels derived from human adipose tissue have also been used to assess exposure.<sup>47</sup> Moreover, levels of TCDD and/or other PCBs in human breast milk from Vietnamese women, and food and soil from Vietnam<sup>50–57</sup> have been examined to study the health of individuals who resided in or around "hot spots" (US military base locales where herbicides were stored and handled)<sup>58</sup> or "spray areas".

Despite the many different PCDDs that exist, TCDD is the only dioxin congener found in AO<sup>45</sup> and thus has been typified as a marker for AO exposure. Although service-related exposures occurred decades ago during the War, dioxin's lipophilicity accounts for its long-term retention in human adipose tissue and its estimated median 7.1 year half-life (95% CI about the median of 5.8 to 9.6 years)<sup>59</sup>; these characteristics also contribute to its utility as a surrogate measure of past herbicide exposure in Vietnam. However, research findings on the relationship of serum dioxin with perceived self-reported spray exposure have been mixed. Self-reported AO exposure was not associated with serum TCDD levels of Korean Vietnam veterans ( $n = 102$ )<sup>44</sup> and US Army enlisted combat Vietnam veterans (where highly, occupationally exposed veterans were not targeted and most of the self-reported herbicide exposure from military service was indirect, eg, clearing vegetation from sprayed areas or walking through sprayed areas).<sup>40</sup> But, in another study, veterans of the US ACC who reported that they sprayed/handled AO in Vietnam ( $n = 357$ ) exhibited almost a twice higher level of serum TCDD compared with members of the ACC who did not spray/handled herbicides

in Vietnam ( $n = 413$ ) (mean [range] = 4.3 (0.5 to 85.8) ppt vs. 2.7 ppt [0.6 to 27.7],  $P < 0.001$ ).<sup>14</sup>

The ACC is the largest cohort of Vietnam War veterans most directly exposed to AO and other herbicides in Vietnam, and it is this population that represents our best opportunity to improve our understanding of the adverse health effects of these exposures.<sup>60</sup> Few studies have targeted the risk of hypertension in Vietnam era veterans and above all, hypertension in veterans with military service-related herbicide exposures.

The objective of this analysis was to investigate the association between exposure to herbicides and the risk of hypertension among ACC veterans who were involved in chemical operations and either served in Vietnam or elsewhere during the Vietnam War.

## METHODS

### Cohort Development

An original cohort of 5609 Vietnam era ACC veterans<sup>15</sup> was screened for eligibility into the current study (Fig. 1). ACC veterans were identified based on a review of morning reports of ACC units stationed in Vietnam, Defense Manpower Data Center tapes of Vietnam era Army personnel with military occupational specialty (MOS) codes showing chemical operations involvement between 1971 to 1974 and 1965 to 1971 class rosters from the Army Chemical School in Ft. McClellan, AL.<sup>10,15</sup> Using military personnel records from the National Personnel Record Center (NPRC, US National Archives and Records Administration, St. Louis, MO), the listing of eligible veterans was restricted to men who had a minimum of 18 months active US Army service from July 4, 1965 to March 28, 1973.<sup>15</sup> Further details about cohort development are published elsewhere.<sup>10,15</sup>

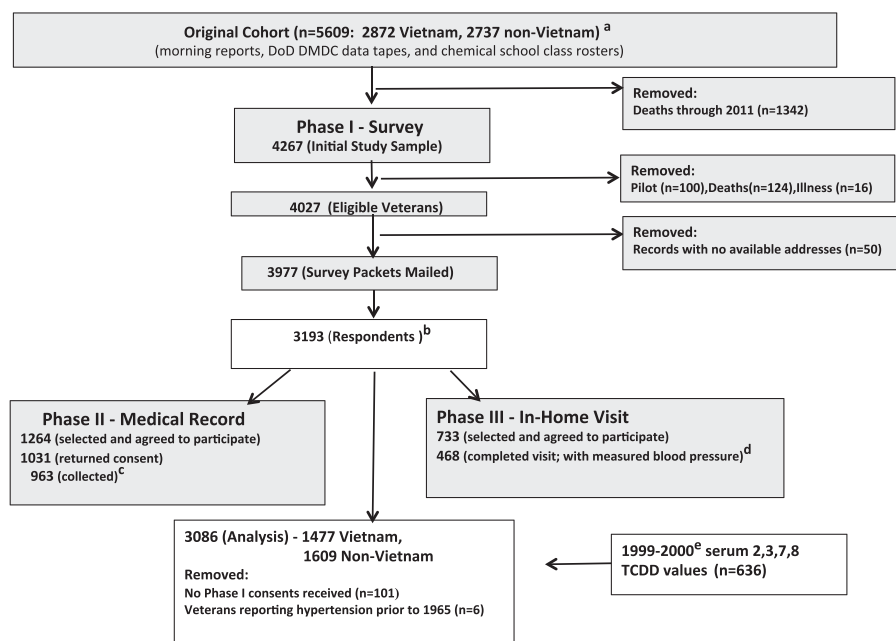
Vital status was determined through October 2011 using the Department of Veterans Affairs (VA) Beneficiary Identification and Records Locator Subsystem Death File and the Social Security Administration Death Master File. The main study excluded deceased ( $n = 1466$ ), those who were too ill to participate ( $n = 16$ ), and veterans ( $n = 100$ ) who participated in two pilot studies (April to December, 2012). Eligible participants totaled 4027. The study and informed consent procedures were approved by the Washington, DC VA Medical Center Institutional Review Board.

### Data Collection

The survey (mail or computerized assisted telephone interview), medical records review/abstraction, and in-home examination study phases were administered between January and December 2013. An initial survey packet, reminder postcard, and two additional packets were mailed. Addresses were mainly identified from the Internal Revenue Service Taxpayer Address Retrieval System through the National Institute for Occupational Safety and Health and Accurant LexisNexus. Survey packets were sent to 3977 veterans after removing 50 who had no available addresses (Fig. 1). Informed consent was obtained from participants for all three study phases. Monetary incentives were provided for all phases (including pilots)—small cash incentives (\$2 included with each mail questionnaire and \$5 cash included with a refusal conversion mail questionnaire), \$50 check (for a completed and returned mail questionnaire or medical record consent form), and \$100 (for a completed in-home blood pressure [BP] measurement by a medical technician).

Physician-diagnosed hypertension was obtained from the survey based on whether a veteran reported that a doctor, nurse, or healthcare professional ever told the veteran that he had high blood pressure or hypertension (self-reported physician-diagnosed hypertension [SRH]). Response options were "Yes", "No", or "Told borderline high/pre-hypertensive" (latter were classified as

**FIGURE 1.** Cohort development and data collection phases, ACC Vietnam Era Veterans Health Study 2013. ACC, Army Chemical Corps.; DoD DMDC, Department of Defense Defense Manpower Data Center; n, number; TCDD, 2,3,7,8 tetrachlorodibenzo-p-dioxin. <sup>a</sup>Thomas and Kang<sup>10</sup>, Dalager and Kang<sup>15</sup>. <sup>b</sup>Participation rate of 79.3% of eligible Veterans. <sup>c</sup>Participation rate of 93.4% of consents received. <sup>d</sup>Participation rate of 63.8% of those selected. <sup>e</sup>Kang et al<sup>14</sup>.



borderline hypertensives). Antihypertensive medication use was based on a “yes” response to the survey question: “Are you currently taking medicine for your high blood pressure or hypertension?” Veterans were also asked “In what year did a doctor, nurse, or health professional first tell you that you had high blood pressure or hypertension?” In addition to those who responded “yes” to being told by a health professional that they were hypertensive, veterans who were told they were borderline hypertensive, and those who did not report hypertension but reported taking antihypertensive medications (medicated hypertensives) were classified as hypertensive and included in the definition of hypertension prevalence. Borderline hypertensives were included in this definition because being male, having comorbid conditions (eg, diabetes, metabolic syndrome, sleep disorders), and having variable BPs (that increases with age) are associated with a greater likelihood of masked hypertension.<sup>61</sup>

Self-reported herbicide-spray-status was obtained from “yes/no” responses to the survey questions: “Now thinking about herbicides, did you yourself ever mix, handle, or spray these chemicals while you were in the military?”, “Now thinking only about herbicide spray equipment or containers of herbicide, did you ever handle them while in the military?” Self-reported spray status was used as a surrogate measure of herbicide exposure because of the association found between blood serum dioxin levels and self-reported herbicide spraying in earlier research on the ACC<sup>14</sup> and because no documentation of individual-level spray activity exists. Blood serum TCDD (ppt or pg/g lipid) collected in the 1999 to 2000 health survey<sup>14</sup> of these same ACC veterans was used to verify self-reported exposure because collection of current serum TCDD samples was not feasible due to the large amount of time that had passed since exposure. Of the 883 ACC veterans for whom TCDD values were obtained in 1999 to 2000, 636 (72%) participated in the current study. In 1999 to 2000, blood specimens were collected at veterans’ homes by trained medical technicians. A CDC laboratory analyzed the specimens using gas chromatographic and high resolution mass spectrometric methodologies<sup>62</sup> to identify 2,3,7,8-TCDD and six other dioxin congeners. Only those Army personnel who were

designated as having a chemical operations MOS during the Vietnam era were included in the current study. TCDD levels in veterans were only a means of assessing the strength of the self-reported history of exposure to herbicide between Vietnam veterans and a group of non-Vietnam veterans who served in the ACC during the War.

The covariates collected from the survey were age at time of survey, race/ethnicity (reclassified as White/nonwhites), alcohol use in past 30 days (drinks per day – heavy, > 2; moderate/light, 1-2)<sup>63,64</sup> and tobacco use<sup>63</sup> [cigarette smoking (current, former, never), other tobacco product use (every day, some days, not at all)], and body mass index (BMI) (<18.5, 18.5 to 24.9, 25.0 to 29.9, ≥30.0).<sup>63</sup> BMI, age, race/ethnicity, tobacco use, and excessive alcohol intake are established risk factors for hypertension.<sup>65</sup> Vietnam-service-status (served in Vietnam or not in Southeast Asia) and military rank (officer/enlisted) was previously obtained from military personnel record data from the NPRC.<sup>10,15</sup>

Survey respondents who provided a valid informed consent and a completed survey were assigned to an in-home examination and/or a medical records review by exposure (stratified by Vietnam-service-status and self-reported herbicide spraying/distribution status). Stratum-level quotas were established to assure maximal representation by exposure status but random selection and assignment were not employed in these two phases to satisfy cell size and geographic limitations.

Medical record data were used to confirm SRH. Record abstraction was completed by experienced personnel and led by a study-team physician. Medical record entries were made using a standardized form, verified by a second abstractor, and discrepancies resolved by a third abstractor. Hypertension was identified from medical records if at least one of eight episodes of care mentioned hypertension; whereas borderline hypertension was identified if at least one episode was described as borderline. Mention of hypertension and its description (eg, borderline, essential) were provided in the abstracted information.

In-home BP measurements were also used to verify SRH. In-home examinations were conducted by 14 experienced and trained technicians who visited veterans’ homes nationwide to take BP and



other measurements. Measurement procedures were based on American Heart Association clinical practice guidelines.<sup>66</sup> The technicians measured BP three times during a 5-minute interval using the Omron HEM-780, Omron Healthcare Inc (Lake Forest, IL) automatic digital sphygmomanometer with a manual cuff that encircled at least 80% of the participant's arm. BP readings were done on the left arm bared with the participant resting quietly in a chair, legs and ankles uncrossed, feet flat on the floor, and back supported against the chair. Arms were set resting comfortably on a chair's arms or table so that the cuff was at the same level as the participant's heart. The examination was terminated if two of the three measurements resulted in an extreme systolic blood pressure (SBP) ( $\geq 160$  mm Hg) or diastolic blood pressure (DBP) ( $\geq 110$  mm Hg), or any SBP exceeded 200 mm Hg. Technicians recorded BP readings, anthropometrics (eg, height, weight), demographics (age, race/ethnicity), and precautions (caffeine/smoking cessation 1 hour prior to BP measurement).

### Statistical Analysis

Of the 3193 respondents, data on 3086 veterans were used for analysis because veterans who did not return a mail survey consent ( $n = 101$ ) and those self-reporting hypertension prior to 1965 ( $n = 6$ ) were excluded. Statistics presented in this paper were generated using SAS<sup>®</sup> software, version 9.4, SAS Institute Inc (Cary, NC).<sup>67</sup> Two-tailed statistical tests were conducted and  $P$  values  $\leq 0.05$  were considered statistically significant.

Descriptive statistics were used. Chi-squared tests were performed to assess two-way, unadjusted associations between variables. Using multiple logistic regression (SAS PROC LOGISTIC), the association between SRH and herbicide-spray-status was examined while controlling for Vietnam-service-status, military rank, age, tobacco/alcohol use, race, and BMI. Tolerances were computed to assess multicollinearity, interactions evaluated, and adjusted odds ratio (ORs) with 95% CIs reported. Partial regression coefficients and related multivariable statistics were evaluated. Regressions were based on 2903 records because of missing observations on model variables. The effects of herbicide-spraying and Vietnam-service-status on SRH were evaluated separately as single variables and then in tandem as one variable.

Arithmetic mean differences in measured BPs by self-reported hypertension status and serum TCDD values by military service location were tested using  $t$  tests or  $F$  tests (analysis of variance [ANOVA]). For  $t$  tests, we used either the Satterthwaite or pooled variance tests. Contrasts were performed to compare means for hypertension/medication use by SBP and DBP. Indices of agreement between self-reports and medical records included overall agreement, positive and negative agreement,<sup>68</sup> Cohen's kappa ( $\kappa$ ) with 95% CI,<sup>68</sup> and prevalence- and bias-adjusted (PABAK) kappa.<sup>69</sup> Variance estimates for kappa were based on Fleiss<sup>70</sup> and strength of concordance based on published recommendations.<sup>71</sup> For the in-home measured blood pressures, the mean of three trials was obtained for each veteran for SBP and DBP, respectively, and then overall means calculated for SBPs and DBPs by SRH level (with and without medication). In analyses involving comparisons of these data sources, borderline hypertensives were removed ( $n = 45$ , medical records;  $n = 25$ , measured blood pressure from in-home examinations) because their inclusion may obscure differences between means or agreement.

### RESULTS

Of 3977 veterans surveyed, 80.3% responded ( $n = 3193$ ) (Fig. 1). Of the 1264 veterans who were originally selected for the medical records review and agreed to have their healthcare providers contacted, 1031 (81.6%) returned a signed consent. Providers returned medical records for over 90% of the veteran-provided consents ( $n = 963$ ). Nearly two-thirds of the in-home

examinations for the 733 veterans selected for this study phase were also completed ( $n = 468$ ).

Demographic, military, and health characteristics for Vietnam and non-Vietnam veterans are presented in Table 1. Most veterans were between the ages of 60 and 69 (median = 65.0), white, and were enlisted personnel. A higher percentage of Vietnam veterans were 70 years of age or older (19.7%) than non-Vietnam veterans (7.6%). Herbicide spraying was higher among Vietnam (62.0%) than non-Vietnam veterans (28.0%). About 72% of Vietnam veterans were current or former smokers compared with 64% of non-Vietnam veterans.

Hypertension prevalence by Vietnam-service-status and herbicide-spray-status is reported in Table 2. The prevalence of SRH among Vietnam veterans was 78.0% and 68.2% for non-Vietnam veterans. The prevalence of SRH was the highest among Vietnam sprayers (81.6%) followed by non-Vietnam sprayers (77.4%), Vietnam nonsprayers (72.2%), and non-Vietnam nonsprayers (64.6%).

Mean serum 2,3,7,8 TCDD values are reported in Table 3 by Vietnam-service-status and herbicide-spray-status. Mean serum TCDD levels were significantly higher among Vietnam-herbicide-sprayers (mean = 3.5 ppt, range = 0.5 to 30.6) compared with Vietnam-nonsprayers (mean = 2.5 ppt, range = 0.7 to 17.7) ( $P = 0.0001$ ). No statistically significant differences in mean TCDD values were observed between non-Vietnam-sprayers (mean = 2.4 ppt, range = 0.7 to 9.6) and nonsprayers (mean = 2.2 ppt, range = 0.4 to 12.5) ( $P = 0.69$ ). Mean TCDD levels were highest for Vietnam-sprayers and lowest for non-Vietnam-nonsprayers.

Table 4 presents multiple logistic regression results. Herbicide-spray-history was significantly and independently related to SRH ( $P < 0.0001$ ) as well as Vietnam-service-status ( $P = 0.01$ ). The odds of hypertension among sprayers was estimated to be 1.74 [1.44,2.11] times the odds among nonsprayers; whereas the odds of hypertension among those who served in Vietnam was 1.26 [1.05,1.53] times the odds among non-Vietnam veterans. Among Vietnam-service veterans, the odds of hypertension for sprayers was 77% higher than the odds for nonsprayers ( $OR_{adjusted} = 1.77$  [1.35,2.30]); likewise for those with no Vietnam service, the OR was still significantly elevated comparing sprayers and nonsprayers ( $OR_{adjusted} = 1.72$  [1.31,2.26]). The association with SRH was highest when comparing Vietnam sprayers to non-Vietnam nonsprayers ( $OR_{adjusted} = 2.21$  [1.76,2.77]). The lowest OR fell below 1.0 for men who may have had little or no spray involvement (Vietnam-service-nonsprayers and non-Vietnam-sprayers;  $OR_{adjusted} = 0.73$  [0.53,0.99]).

Table 5 provides estimates of mean measured BPs by SRH. Mean SBP was significantly greater ( $t[307.1] = 3.71$ ,  $P = 0.0002$ ) for ACC veterans with SRH (mean = 134.2 mm Hg, standard deviation [SD] =  $\pm 17.0$  mm Hg) than for those without SRH (mean SBP = 128.5 mm Hg, SD =  $\pm 13.7$  mm Hg). Measured SBP was highest for those reporting hypertension with no medication (mean = 138.6 mm Hg, SD =  $\pm 19.5$  mm Hg) and lowest for non-hypertensives (mean SBP = 128.5 mm Hg, SD =  $\pm 13.7$  mm Hg) ( $P = 0.0007$ ). All paired comparisons of differences in mean SBP between veterans having hypertension without medication, hypertension with medication, and no hypertension were statistically significant ( $P \leq 0.003$ ), except for the comparison of nonmedicated hypertensive veterans and medicated hypertensives ( $P = 0.07$ ). Mean DBPs for nonmedicated hypertensives were significantly higher than mean DBPs for veterans without hypertension ( $P = 0.03$ ). Mean SBPs and DBPs declined progressively with SRH level.

Agreement between BP reported in medical records and SRH is presented in Table 6. The percentage of overall agreement between SRH and medical records was almost perfect<sup>71</sup> (89%). Kappa (unadjusted for bias, prevalence) was 0.72 (95% CI: 0.67,0.77), and positive and negative agreements were 0.92 and

**TABLE 1.** Characteristics, ACC Veterans by Vietnam-Service-Status

Characteristic	Vietnam-Service-Status						P <sup>b</sup>
	All (n = 3,086)		Vietnam <sup>a</sup> (n = 1,477)		Non-Vietnam <sup>a</sup> (n = 1,609)		
	n, %						
Age group, y, at time of survey <sup>d</sup>							<0.0001*
<60	98	3.2	5	0.3	93	5.8	
60–69	2,552	83.4	1,171	79.9	1,381	86.5	
70–79	372	12.2	252	17.2	120	7.5	
≥80	39	1.3	37	2.5	2	0.1	
Median age, y, at time of survey <sup>c,d</sup>	65		66		64		
Race <sup>d</sup>							0.02*
White	2,341	76.4	1,095	74.4	1,246	78.2	
Nonwhite	724	23.6	376	25.6	348	21.8	
Herbicide-sprayer-status <sup>d</sup>							<0.0001*
Yes	1,365	44.2	915	62.0	450	28.0	
No	1,721	55.8	562	38.0	1,159	72.0	
Rank <sup>a</sup>							<0.0001*
Officer	338	11.0	123	8.3	215	13.4	
Enlisted	2,748	89.0	1,354	91.7	1,394	86.6	
Cigarette-smoking status <sup>d</sup>							<0.0001*
Current smoker	548	18.0	264	18.2	284	17.9	
Former smoker	1,520	50.0	786	54.1	734	46.1	
Nonsmoker	975	32.0	402	27.7	573	36.0	
Other tobacco product use <sup>d</sup>							0.76
Every day	167	5.5	81	5.6	86	5.4	
Some days	106	3.5	47	3.2	59	3.7	
Not at all	2,777	91.0	1,330	91.2	1,447	90.9	
Alcohol use in the past 30 days <sup>d,e</sup>							0.01*
Heavy	303	10.0	133	9.2	170	10.8	
Moderate/light	1,428	47.3	655	45.4	773	49.1	
No alcohol	1,286	42.6	655	45.4	631	40.1	
BMI, kg/m <sup>2,d</sup>							0.23
<18.5	26	0.9	12	0.8	14	0.9	
18.5–24.9	641	21.0	303	20.7	338	21.3	
25.0–29.9	1,311	43.0	607	41.5	704	44.4	
≥30.0	1,072	35.2	541	37.0	531	33.4	

% , percent; ACC, Army Chemical Corps; BMI, body mass index; kg/m<sup>2</sup>, kilograms/(meters)<sup>2</sup>; n, number; y, years.

\*Statistically significant.

<sup>a</sup>Military personnel records.

<sup>b</sup>P values based on chi-squared test statistic.

<sup>c</sup>25th and 99th percentiles for “Vietnam” are 64 and 82, respectively; for “non-Vietnam,” 62 and 74, respectively.

<sup>d</sup>2013 survey.

<sup>e</sup>Drinks per day - heavy (> 2), moderate/light (1-2)

**TABLE 2.** Prevalence of Self-Reported Physician-Diagnosed Hypertension, by Vietnam-Service-Status

Characteristic	All	Hypertension <sup>a</sup>			
		Yes		No	
		n	%	n	%
All	3,068	2,236	72.9	832	27.1
Vietnam-service-status					
Vietnam					
All	1,469	1,146	78.0	323	22.0
Herbicide sprayer	907	740	81.6	167	18.4
Nonsprayer	562	406	72.2	156	27.8
Non-Vietnam					
All	1,599	1,090	68.2	509	31.8
Herbicide sprayer	446	345	77.4	101	22.7
Nonsprayer	1,153	745	64.6	408	35.4

% , percent; n, number.

<sup>a</sup>Missing (n = 18).

**TABLE 3.** Mean Serum 2,3,7,8 TCDD (Dioxin) Concentrations (Range)<sup>a</sup>, by Vietnam-Service-Status and Self-Reported Herbicide Spray History

Vietnam-Service-Status	Herbicide Spray History		P
	Yes	No	
Yes (n = 553)	3.5 (0.5–30.6) n = 361	2.5 (0.7–17.7) n = 192	P = 0.0001
No (n = 83)	2.4 (0.7–9.6) n = 25	2.2 (0.4–12.5) n = 58	P = 0.69
All (n = 636)	n = 386	n = 250	

n, number; TCDD, tetrachlorodibenzo-p-dioxin.

<sup>a</sup>Measured in parts per trillion (ppt), lipid corrected (pg/g). 2013 survey respondents who have 1999–2000 (Kang et al<sup>14</sup>) serum TCDD values.

0.80, respectively. PABAK (0.77; bias index = 0.01, prevalence index = 0.44) varied little from the unadjusted kappa. Concordance estimates varied minimally across levels of herbicide-spray-status and Vietnam-service-status.

## DISCUSSION

This study demonstrates a significant association between herbicide exposure and hypertension risk, and the same for military service in Vietnam and hypertension risk. The current study, the prior ACC studies,<sup>10,14–16,45</sup> and the Air Force Health Study,<sup>72</sup> represent a compendium of studies that extend our knowledge of the long-term health consequences of military service and herbicide exposure during the Vietnam War.

Several points provide support for our findings: (1) self-reported herbicide-spray-status is supported by serum TCDD levels of study participants obtained many years before the current survey. The highest mean serum TCDD level was observed among Vietnam-service-sprayers and the lowest mean level was shown for non-Vietnam-nonsprayers; (2) service location, rank, and chemical operations MOS of the veteran participants were ascertained from military personnel files; (3) Self-reported hypertension status was verified through in-person blood pressure measurement by trained technicians and a review of medical records for a sample of study participants. There was near perfect agreement between self-reported hypertension and medical history listed in medical records; and (4) important, measurable risk factors like BMI, smoking, alcohol, and race were controlled for by multivariable statistical analyses.

The current study tried to address the limitation of unmeasured exposures of concern and potential confounders by carefully selecting a control group of veterans who were similar to members of the study group with respect to branch of service, length of service, time period of service, and military occupation<sup>45</sup> except for their military service in Vietnam. Moreover, the overall survey response rate for the current study was high, which suggests generalizability of findings to the approximately 4000 eligible ACC veterans and applicability to possibly other Vietnam veterans who may have had similar exposures (eg, Navy riverine patrols, engineering personnel, or those involved in AO removal or defoliation testing operations).<sup>1,9</sup> To the best of our knowledge, the ACC personnel listings used to identify subjects in this cohort represent the most comprehensive enumeration of Army Vietnam veterans whose occupational specialty was chemical operations.

Prior research on the ACC and the AFRH personnel show varying results regarding hypertension-related mortality. Two studies of ACC veteran mortality showed no significant excess mortality risk due to circulatory disease or hypertension for Vietnam veterans relative to non-Vietnam veterans<sup>15,16</sup>; while there was a significantly increased circulatory disease mortality risk for AFRH ground personnel when compared to an unexposed control group<sup>17,18</sup>. Small

**TABLE 4.** Odds Ratios and 95% Confidence Intervals, Multiple Logistic Regression

Characteristic	OR (95% CI)	P
Herbicide sprayer (ref = nonsprayer) <sup>a</sup>	1.74 (1.44, 2.11)*	<0.0001*
Vietnam service (ref = no Vietnam service)	1.26 (1.05, 1.53)*	0.01*
Vietnam-service-status/ herbicide-sprayer-status <sup>b</sup>		<0.0001*
Vietnam sprayers vs. Vietnam nonsprayers	1.77 (1.35, 2.30)*	
Non-Vietnam sprayers vs. non-Vietnam nonsprayers	1.72 (1.31, 2.26)*	
Vietnam sprayers vs. non-Vietnam sprayers	1.29 (0.95, 1.74)	
Vietnam nonsprayers vs. non-Vietnam nonsprayers	1.25 (0.99, 1.59)	
Vietnam nonsprayers vs. non-Vietnam sprayers	0.73 (0.53, 0.99)	
Vietnam sprayers vs. non-Vietnam nonsprayers	2.21 (1.76, 2.77)*	
Enlisted personnel (ref = officer)	1.10 (0.84, 1.45)	0.49
Age group, at time of survey (ref = <60 y)		0.69
60–69	1.03 (0.63, 1.68)	
70–79	1.06 (0.61, 1.85)	
≥80	1.87 (0.62, 5.59)	
Nonwhite (ref = White)	1.97 (1.56, 2.48)*	<0.0001*
Cigarette smoking status (ref = nonsmoker)		0.01*
Current smoker	0.93 (0.72, 1.21)	
Former smoker	1.27 (1.04, 1.55)*	
Other tobacco product use (ref = none)		0.67
Daily	1.00 (0.68, 1.45)	
Some days	1.26 (0.76, 2.10)	
Alcohol use (ref = none)		0.005*
Heavy (> 2 drinks/day)	1.40 (1.02, 1.92)*	
Moderate/light (1–2 drinks/day)	0.85 (0.71, 1.02)	
BMI (ref = normal weight)		<0.0001*
Underweight (<18.5 kg/m <sup>2</sup> )	1.84 (0.70, 4.84)	
Overweight (25.0–29.9 kg/m <sup>2</sup> )	1.71 (1.39, 2.11)*	
Obese (≥30 kg/m <sup>2</sup> )	3.35 (2.63, 4.26)*	

BMI, body mass index; CI, confidence interval; kg/m<sup>2</sup>, kilograms/(meters)<sup>2</sup>; OR, odds ratio; Ref, referent; y, years.

\*Statistically significant (95% CI does not contain 1.0).

<sup>a</sup>Association of self-reported physician diagnosed hypertension with herbicide-spray-status adjusted for Vietnam-service-status, military rank, age, smoking status, other tobacco use, race, BMI, and alcohol use. Regression based on 2903 observations due to missing (n = 183) on model variables.

<sup>b</sup>Vietnam sprayers, n = 851; Vietnam nonsprayers, n = 535; non-Vietnam sprayers, n = 418; non-Vietnam nonsprayers, n = 1099. Statistics obtained from the regression using a combined spray/service variable.

**TABLE 5.** Self-Reported Physician-Diagnosed Hypertension, Medicated Hypertension Status Versus Measured Blood Pressure

Condition	P <sup>a</sup>	Mean (±SD) SBP	Mean (±SD) DBP
Hypertension (n = 440) <sup>b,c,d</sup>	0.03*		
Yes (n = 307)		134.2 ± 17.0	80.2 ± 10.5
No (n = 133)		128.5 ± 13.7	78.7 ± 10.1
Medicated hypertension status (n = 440) <sup>e</sup>	0.05*		
Hypertension, no medication (n = 38)		138.6 ± 19.5	82.8 ± 12.2
Hypertension, medication (n = 269)		133.6 ± 16.5	79.8 ± 10.2
No hypertension (n = 133)		128.5 ± 13.7	78.7 ± 10.1

% = percentage; CI, confidence interval; DBP, diastolic blood pressure(s); n, number; SBP, systolic blood pressure(s); SD, standard deviation.

<sup>a</sup>Statistically significant.

<sup>b</sup>P value based on chi-squared test statistic representing the association between measured blood pressure (hypertensive [SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg] or not) with self-reported physician-diagnosed-hypertension (SRH) or medicated hypertension status (MHS).

<sup>c</sup>Four hundred sixty six examinations available for analysis after all study exclusions applied. Borderline hypertensives were excluded here (n = 25) and there was one missing on SRH.

<sup>d</sup>SBPs by SRH (t[307.1] = 3.71, P = 0.0002).

<sup>e</sup>DBPs by SRH (t[438] = 1.36, P = 0.17).

<sup>f</sup>All comparisons of mean SBPs by MHS were statistically significant (MHS 1 vs. 3, P = 0.0007; MHS 2 vs. 3, P = 0.003) except for the comparison of MHS 1 versus 2 (P = 0.07). The comparison of mean DBPs for MHS 1 versus 3 was statistically significant (P = 0.03), but not significant for the remaining two comparisons (MHS 1 vs. 2 [P = 0.09], MHS 2 vs. 3 [P = 0.32]).

numbers of hypertension deaths and lack of adjustment for key covariates were limitations here. The relationship between herbicide spraying and hypertension mortality was studied in a 2010 published report of ACC veterans<sup>16</sup> where findings were adjusted for smoking status and other covariates, but the observed elevated risk (Relative Risk<sub>adjusted</sub> = 2.35 [0.19,28.52]) was based on three deaths, and only on those veterans with Vietnam Service who supplied responses on spraying history from a 1999 to 2000 ACC health study (n = 1473; approximately 25% of the original cohort).<sup>14</sup> Hypertension-related mortality outcomes may also be underestimated in these studies if hypertension is not listed as a cause of death on death certificates,<sup>73</sup> particularly for older veterans who may have multiple comorbidities.<sup>74</sup> In other research, herbicide exposure assessed by the exposure opportunity index (EOI)

GIS-based model<sup>43</sup> had no association with hypertension mortality<sup>22</sup> or morbidity.<sup>23,39</sup>

A study of US Army veterans indicated a clear ‘dose–response’ relationship between perceived herbicide exposure and reported health conditions<sup>75</sup> (eg, the greater the perceived exposure, the greater reporting of health conditions). Similarly, a Korean study of Vietnam veterans showed that the prevalence of self-reported hypertension monotonically increased with the levels of perceived self-reported exposure to AO (test for trend, P < 0.001).<sup>39</sup> We have ruled out a bias from self-reported exposure and outcome data collected in this study because of (1) the almost perfect agreement<sup>71</sup> found between self-reported hypertension and medical record data. The result of the medical record review was comparable to results cited in other studies of older men—either US nonveterans

**TABLE 6.** Agreement Between Self-Reported Physician-Diagnosed Hypertension and Medical Records<sup>a</sup>

Condition	MR (+) <sup>b</sup> , SR (+)	MR (-) <sup>c</sup> , SR (+)	MR (+), SR (-)	MR (-), SR (-)	p <sub>o</sub> <sup>d</sup>	p <sub>e</sub> <sup>e</sup>	K <sub>unadjusted</sub> (95% CI)	p <sub>a</sub> <sup>f</sup>	p <sub>n</sub> <sup>g</sup>	BI <sup>h</sup>	PI <sup>i</sup>	PABAK <sup>j</sup>
Hypertension												
All (N = 905)	599	57	46	203	0.89	0.60	0.72 (0.67, 0.77)*	0.92	0.80	0.01	0.44	0.77
Sprayer status												
Sprayers (N = 467)	324	33	21	89	0.88	0.62	0.69 (0.61, 0.77)*	0.92	0.77	0.03	0.50	0.77
Nonsprayers (N = 438)	275	24	25	114	0.89	0.57	0.74 (0.67, 0.81)*	0.92	0.82	0.00	0.37	0.78
Vietnam-service-status												
Vietnam (N = 580)	385	38	31	126	0.88	0.60	0.70 (0.64, 0.77)*	0.92	0.79	0.01	0.45	0.76
Non-Vietnam (N = 325)	214	19	15	77	0.90	0.59	0.75 (0.67, 0.83)*	0.93	0.82	0.01	0.42	0.79

ACC, Army Chemical Corps.; MR, medical record; SR, self-report; k, kappa; BI, bias index; PI, prevalence index; PABAK, prevalence adjusted bias adjusted kappa; CI, confidence interval; n or N, number.

<sup>a</sup>Nine hundred sixty two medical records were analyzed after study exclusions applied. n = 4, missing on self-reported physician-diagnosed hypertension (SRH). Borderline hypertensives were excluded here (n = 53; 45 reported as borderline hypertensive based on SRH and eight as borderline from MR).

<sup>b</sup>(+) presence of condition.

<sup>c</sup>(-) absence of condition.

<sup>d</sup>Observed agreement (proportion) = p<sub>o</sub> = (a + d)/N. Overall agreement (%) = p<sub>o</sub> × 100. Cells a = +/+, b = -/+, c = +/-, d = -/-.

<sup>e</sup>Expected agreement (proportion) = p<sub>e</sub> = [(a + b)(a + c) + (c + d)(b + d)]/N<sup>2</sup>.

<sup>f</sup>Positive agreement (proportion) = p<sub>a</sub> = 2a/(N + a - d).

<sup>g</sup>Negative agreement (proportion) = p<sub>n</sub> = 2d/(N - a + d).

<sup>h</sup>Bias index = |(b - c)/N.

<sup>i</sup>Prevalence index = |(a - d)/N.

<sup>j</sup>Prevalence-adjusted-bias-adjusted kappa = 2p<sub>o</sub> - 1.

\*Statistically significant. H<sub>0</sub>: k = 0 (agreement is purely by chance).



( $k = 0.71$ ; age  $>65$  years)<sup>76</sup> or VA healthcare users ( $k = 0.70$ ; mean age = 64 years)<sup>77</sup>; and (2) 1999 to 2000 serum TCDD values that are relatively comparable to other Vietnam era veteran studies given TCDD's half-life—blood specimens sampled in 1986 to 1987 by the CDC<sup>40</sup> ( $n = 646$ , mean[range] = 4.2 [0 to 45] pg/g lipid) in US Army Vietnam veterans, 1987-sampled blood specimens for AFRH personnel<sup>48</sup> ( $n = 888$ , median, 12.4 pg/g lipid) for whom extrapolated mean serum TCDD levels at time of exposure were in excess of those calculated for ACC veterans, and serum TCDD collected in 2002 on AFRH personnel and a comparison group of veterans who served in Southeast Asia during the same time<sup>46</sup> that were higher but still within range of ACC 1999 to 2000 values.<sup>14</sup> Mean serum TCDD was 9.5 ppt (lipid based) in Ranch Hands<sup>46</sup> and 4.3 ppt in ACC Vietnam-service sprayers,<sup>14</sup> but mean serum TCDD for the comparison groups in the AFRH<sup>46</sup> and ACC<sup>14</sup> studies were closer—2.5 ppt and 2.1 ppt, respectively.

Moreover, expectations for 2012 to 2013 self-reported spraying paralleled 1999 to 2000<sup>14</sup> TCDD serum levels because we found good correspondence between self-reported herbicide spraying and serum TCDD levels. Past studies<sup>14,45</sup> based on the same cohort demonstrated a strong relationship between self-reported spraying and serum dioxin levels among Vietnam era ACC veterans. In a pilot study, ACC Vietnam self-reported herbicide sprayers had significantly higher ( $P = 0.05$ ) concentrations of serum TCDD than non-Vietnam-nonsprayers, while no significant group differences were found in six other serum dioxin congeners.<sup>45</sup> In more recent research, median TCDD levels among herbicide-exposed AFRH personnel were more than double the levels observed for a comparison unexposed veteran group,<sup>46</sup> and similar to the Army Chemical Corps study,<sup>45</sup> levels for other congeners were comparable between the exposed and unexposed groups. But among Vietnam War veterans overall (non-ACC veterans), a 1991 published study<sup>78</sup> found no difference in mean 2,3,7,8-dioxin levels derived from adipose tissue for Vietnam, non-Vietnam, and civilian controls. These results were consistent with VES findings.<sup>40</sup>

The National Health and Nutrition Examination Surveys 1999 to 2004 and 2007 to 2010 found hypertension for US male adults 65 years of age or older was 63.0%<sup>79</sup> and 71.6%,<sup>80</sup> respectively. Hypertension prevalence among older (mean = 67.0 years), mainly male US veterans was 64.0%.<sup>81</sup> The prevalence found among non-Vietnam veterans (median = 64.0 years) was similar to US adults 65 years or older and other older veterans. Of approximately 850,000 VA medical center patients (aged 54 to 64 years) with BPs obtained between 2000 and 2010, 69.1% were hypertensive.<sup>82</sup> Estimates may vary due to differences in the definition of hypertension, data collection methods (eg, self-reports vs. actual physical measurement), or other differences in population risk factors (eg, age) and exposures or comorbidities experienced during an individual's lifetime or military service. ACC prevalence estimates fall within the range of other US men of similar ages, which further strengthens the reliability of a history of SRH.

Our study has limitations. Causal relationships cannot be inferred because this study was cross-sectional. It should be noted that exposure and outcome prevalences for nonrespondents and deceased veterans may differ from study respondents, but our high response rates make bias less likely. Current data collection did not include other risk factors like diabetes, family history of hypertension, and dietary intake (eg, sodium, fat) other than alcohol. These variables were not evaluated and their impact on the resultant association unknown.

This study is also limited by the lack of documentation about the exact type and quantity of the various chemicals these ACC veterans were possibly exposed to during the War. These may include insecticides like malathion, other tactical herbicides (Agent Blue and TCDD-contaminated formulations including Agents Pink, Purple, and Green),<sup>9</sup> diesel and jet fuels, cleaning solvents, tear gas,

napalm, illicit drugs, and antimalarial medications.<sup>1,10,83</sup> For ACC personnel who mainly operated in and around US military bases (unlike ground troops), we considered the risk of exposure from local food sources in Vietnam or contact with sprayed foliage to be low relative to their repeated occupational handling and spraying of chemicals on base. Furthermore, both the study group and the comparison group of veterans belonged to the Army's chemical operations unit during the same Vietnam War period. Therefore, their exposure to any chemicals outside of Vietnam would likely be similar. Although exposure to a group of dioxin-like compounds (PCDFs or other PCBs) could have contributed to hypertension, the magnitude and extent of their exposure to these compounds was expected not to be very different between the two veteran groups during and after military service. This is supported by research on Vietnam War veterans where it was found that levels for other PCDD and PCDF congeners were not significantly different between Vietnam veterans and non-Vietnam veterans based on serum samples collected post-service.<sup>45–47</sup> This current study was not designed to evaluate the effect of any specific chemical on hypertension risk but to answer whether occupational herbicide exposure and service in Vietnam are associated with hypertension risk in these veterans.

We did not include mental health as a covariate. Stress may be a possible contributor to the health effects observed in occupational<sup>28</sup> and military studies.<sup>75,84</sup> Combat-related stress, an important component of the "Vietnam Experience",<sup>83</sup> may have contributed to the effect on SRH that was observed when Vietnam-service-status and spray-history were examined together ("Vietnam sprayers vs. non-Vietnam nonsprayers",  $OR_{adjusted} = 2.21$  [1.76, 2.77])—an effect that was larger than the independent effects of these two variables on hypertension risk. Vietnam combat veterans with post-traumatic stress disorder showed greater increases in BP than noncombat controls when exposed to combat-related stimuli.<sup>85</sup> Significant associations between post-traumatic stress disorder and cardiovascular mortality have been reported for Vietnam veterans post-service.<sup>86</sup>

In conclusion, we found evidence that herbicide exposure and Vietnam service are independently associated with an increased risk of hypertension among a cohort of the Army Chemical Corps Vietnam era veterans. Vietnam veterans constitute a significant percentage of the US aging population and hypertension is a major risk factor for heart disease and stroke.<sup>65</sup> This aging cohort and possibly all veterans potentially exposed to herbicides and rigors of the Vietnam War warrant special attention by their healthcare providers to detect and treat hypertension and manage its sequelae.

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