Published in final edited form as:
Prev Med. 2010 ; 50(5-6): 277–281. doi:10.1016/j.ypmed.2010.02.009.

Military Combat and Burden of Subclinical Atherosclerosis in Middle Aged Men: The ARIC Study

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Abstract

Background—Studies of the cardiovascular consequences of combat stress are few and inconclusive.

Objective—The association between combat exposure and subclinical atherosclerosis at Atherosclerosis Risk in Communities (ARIC) Study visits 1 (1987-1989) and 2 (1990-1992) was assessed among 5,347 men from four U.S. communities.

Methods—Measured an average of 36 years after military entry, carotid intima-media thickness (CIMT) and carotid plaque among non-combat veterans (n=2,127) was compared with non-veterans (n=2,042) and veterans reporting combat experience (n=1,178).

Results—Compared to non-combat veterans, non-veterans (Risk Difference (RD): 10.61; 95% Confidence Interval (CI): 0.81, 20.41) and combat veterans (RD: 12.79; 95% CI: 0.72, 24.86) had higher age-adjusted mean CIMT. Differences remained for combat veterans after adjustment for race, father's education and age at service entry but not years of service and for non-veterans after adjustment for race but not father's education. No differences in carotid plaque were noted.

Conclusion—Results do not suggest that combat has a long-term detrimental effect on subclinical atherosclerosis among men.

Keywords

combat; veteran; subclinical atherosclerosis; plaque; intima media thickness

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Introduction

Stress contributes to the development of cardiovascular disease (CVD) by initiating an inflammatory or atherosclerotic process involving behavioral, neurological, endocrine and immunological components (Labarthe, 1998; Marmot, 1998). Stress experienced by combat veterans can involve continuing psychological and physical consequences.

Epidemiologic evidence, albeit limited, supports a possible effect on increased cardiovascular risk from exposure to military combat (MacLean and Elder, 2007). Combat exposure is associated with higher rates of behavioral problems (Stellman et al., 2000), psychological disorders (Kozaric-Kovacic et al., 2001) and self-reported health conditions (Elder et al., 1997). Most studies have defined combat exposure as a clinical diagnosis of posttraumatic stress disorder (PTSD) or service in a specific war theater and have investigated mortality or self-reported events rather than confirmed incident disease. No significant difference in circulatory disease mortality was found between theater and non-theater Vietnam veterans five, fifteen or thirty years post-service (Centers for Disease Control, 1987; Boehmer et al., 2007). However, veterans with PTSD had higher odds of circulatory disease twenty years post-service (Boscarino, 1997) and higher cardiovascular mortality after thirty years (Boscarino, 2008). Similar results were reported in studies of Gulf War and World War II veterans (Barrett et al., 2002; Falger et al., 2002). Combat-related PTSD has also been associated with increased prevalence of arterial disease (Schnurr et al., 2000) and CHD (Kubzansk, 2007) but not hypertensive or ischemic heart disease (Schnurr et al., 2000).

Studies of the long-term cardiovascular consequences of combat are inconclusive and vary widely in definitions and quality of exposure and outcome data. To date, no studies have assessed the association between combat exposure and subclinical atherosclerosis. We investigate this association in a large, community-based sample of men with service spanning World War II through the Vietnam Conflict.

Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective, community-based study investigating the natural history of CVD and atherosclerosis. At baseline (1987-1989) 15,792 people ages 45-64 years were selected by probability sampling from: Minneapolis, MN; Washington County, MD; Jackson, MS; and Forsyth County, NC. MN and MD participants were white, MS participants were black, and NC included both black and white participants, with black participants over-sampled (ARIC Investigators, 1989; Jackson et al., 1996). Standardized baseline interviews established a health history and obtained demographic, socioeconomic and behavioral risk data. At three follow-up examinations (1990-1992; 1993-1995; 1996-1998), trained, certified technicians performed physical exams and collected cardiovascular measurements. Approximately 94% of survivors were successfully contacted annually to ascertain vital status, health status and hospitalizations. Institutional review boards of collaborating institutions approved the study protocol, and participants provided informed written consent.

The Life Course SES, Social Context and CVD (LC-SES) Study is an ancillary study examining the association between SES across the life course and adult cardiovascular conditions during the 2001-2002 annual telephone follow-up interview (Rose et al., 2004). A total of 12,716 or 81% of the baseline ARIC participants (91% of cohort survivors) participated.

Exclusions

As only 49 women reported military service, and only 5 reported combat exposure, women were excluded (n=7,281). Because we tested modification by race, men with a race other than black or white (n=14) and black men from Washington County or Minneapolis (n=21) were excluded due to small numbers. Also excluded were men with missing or unknown military service status (n=53), leaving a study population of 5,347.

The 414 participants (8% of the study population) with a positive (n=311) or unknown (n=103) history of CHD at baseline were not excluded. Exposure occurred prior to ARIC enrollment and, likely, the inception of measurable subclinical atherosclerosis. Excluding men with more advanced or extensive atherosclerosis could bias results. Analyses were conducted both including and excluding these persons, with little difference in results.

Exposure

Military service was self-reported at the LC-SES interview. Participants reporting service were asked their (1) age at entry into the service and (2) length of service, and whether they (4) served in a combat zone, (5) were ever under fire or fired at the enemy, (6) saw others wounded or killed or (7) were ever wounded or missing in action (Elder and Clipp, 1988). Combat exposure was defined by a positive response to one or more of questions 4-7. A three-level exposure variable was constructed: no history of military service (non-veterans), history of service without to combat (non-combat veterans) and history of service with combat (combat veterans).

Questions 1 and 2 (above) were used to categorize men by era of service: World War II (1941-1945), Korean War (1950-1953) and Vietnam Conflict (1961-1975). Participants' years of service frequently included periods both during as well as preceding, following or falling in between defined eras. Men who served in multiple eras were categorized according to their first. We considered this to be their defining military experience (Elder and Clipp, 1989). Men whose service years did not include those of a defined era were deemed too heterogeneous to categorize separately.

Subclinical Atherosclerosis

Subclinical atherosclerosis measures included carotid intima-media thickness (CIMT) and carotid plaque (Chambless et al., 1997; Hunt et al, 2001). At each ARIC visit, B-mode ultrasound measurements were taken bilaterally at three specific 1-cm segments of the carotid artery within the common carotid, the bifurcation and the internal carotid, for a total of six measurements (Li et al, 1996). CIMT was defined as the average far wall thickness across the six carotid sites. Adjustment for site-specific reader differences and measurement drift across visits and imputation for missing sites was implemented using maximum likelihood techniques for linear mixed models (Chambless et al., 2002). Because CIMT measurement improved over the course of the ARIC study, mean measurements from Visits 1 and 2 were averaged to create a single, mean value to ensure consistency (Li et al., 1996). Plaque was defined as the presence of abnormalities in the arterial wall thickness, shape or texture at one or more of the six sites at Visit 1 or 2, to ensure comparability with CIMT assessment (Hunt et al., 2001).

Risk Factors

Measured at baseline, traditional cardiovascular risk factors included total cholesterol, high density lipoprotein (HDL) cholesterol, self-reported current smoking, diabetes and systolic blood pressure (SBP). Plasma total cholesterol (mg/dL) was measured using established enzymatic methods (Siedel, 1983). HDL (mg/dL) was measured after dextran-magnesium precipitation of non-high density lipoproteins (Warnick et al, 1982). Diabetes was defined as

having a fasting glucose level ≥126 mg/dL, a non-fasting glucose level ≥200 mg/dL or self-reported diabetes diagnosis or diabetic medication use. For SBP (mmHg), three seated measurements were taken with a random-zero sphygmomanometer, and the last two measurements were averaged. Additional baseline risk factors included body mass index (BMI; kg/m^2), body fat distribution (waist circumference; cm), heavy lifetime smoking (≥660 cigarettes/year), current and heavy alcohol use (>210 g/week), physical inactivity (<2 on a 5-point index), low-density lipoprotein (LDL; mg/dL) cholesterol, triglycerides (mg/dL) and prevalent CHD (history of a myocardial infarction (MI), MI according to adjudicated baseline electrocardiograph (ECG) or history of heart or arterial surgery).

Baseline sociodemographic risk factors included age, race, highest level of education (<high school; high school or equivalent; >high school), combined family income (<$25,000; > $25,000) and occupation (managerial/professional; other). Father's education was reported during the LC-SES interview.

Statistical Analyses

Linear regression estimated risk differences (RDs) and 95% confidence intervals (CIs) for CIMT. Although the CIMT distribution is right-skewed, log transformation did not change the back-transformed RD by more than 4%. Thus, we used ordinary least squares regression, which is robust to non-normality of the outcome distribution in large samples (Lumley et al., 2002). Modified Poisson regression estimated risk ratios (RRs) and 95% CIs for carotid plaque (Spiegelman and Hertzmark, 2005).

Estimates were adjusted for young life factors, including age, race, father's education, age at induction and years of service. Because of the likelihood that later life factors (e.g., adult education, smoking, drinking) were involved as intermediates, they were not assessed as confounders (Rothman and Greenland, 1998), as conditioning on intermediates can lead to biased estimates of total effects (Robins, 1989). Interaction by era of service and race was assessed using Wald chi-square tests for plaque and student's t-tests for CIMT, using an *a priori* rejection level of 0.20.

Results

Of 5,347 men, 2,042 (38%) reported no military service, 2,127 (40%) reported service without combat, and 1,178 (22%) reported service with combat. (Table 1) Veterans tended to be older and were more likely to be white than non-veterans. Combat veterans tended to be slightly older than either other group. Non-combat veterans tended to have the highest SES. Mean military induction age differed little between combat and non-combat veterans. Combat veterans tended to serve for longer periods and had a longer mean time since induction.

At baseline, veterans were more likely to be current, heavy drinkers ($p<0.01$) and heavy lifetime smokers ($p<0.01$) than non-veterans but less likely to be current smokers ($p<0.01$) and physically inactive ($p<0.0001$) (Table 2). Combat veterans and non-veterans were most likely to have prevalent diabetes ($p<0.05$), and combat veterans were most likely to have prevalent CHD ($p<0.01$). Groups differed little on BMI or waist circumference, but combat veterans had the highest average total cholesterol ($p<0.05$) and triglycerides ($p<0.05$).

Carotid plaque was more common among combat veterans (54%) and non-combat veterans (48%) compared to non-veterans (45%). (Table 3) Mean CIMT was also greater among combat (802.4 μm; SD: 182.2 μm) and non-combat veterans (757.7 μm; SD: 164.1 μm) compared to non-veterans (745.2 μm; SD: 157.7 μm). Although both veteran groups had significantly less favorable plaque and CIMT profiles than non-veterans in unadjusted analyses, effects were removed or reversed after age-adjustment. Compared to non-combat veterans, both non-

veterans (RD: 10.61; 95% CI: 0.81, 20.41) and combat veterans (RD: 12.79 μm; 95% CI: 0.72, 24.86) had higher age-adjusted mean CIMT. Differences remained in comparisons with combat veterans after adjustment for race, father's education and age at entry but not duration of service and in comparisons with non-veterans after adjustment for race but not father's education. The presence of carotid plaque did not differ among the three groups.

Interaction by era of service and race on RR and RD scales was not significant.

Discussion

An average of 36 years post-service, non-combat veterans had lower age-adjusted CIMT than non-veterans. This is consistent with the “healthy warrior effect,” whereby healthier persons are more likely to be selected for military participation (Haley, 1998). In contrast, combat veterans had significantly higher CIMT than non-combat veterans, even after adjustment for age, race, father's education and age at entry; however, confidence intervals included the null value when duration of service was considered. Carotid plaque frequencies differed little among the three groups. Results do not suggest that combat exposure is associated with increased long-term risk of subclinical atherosclerosis among men.

Earlier studies have reported that combat veterans with PTSD had increased chronic cardiovascular arousal (Buckley et al., 2004), higher circulating catecholamines and other neuroendocrine agents implicated in arterial damage and more frequent abnormal ECG readings (Boscarino and Chang, 1999). Further, veterans with PTSD have higher odds of circulatory disease after twenty years (Boscarino, 1997) and higher cardiovascular mortality (Boscarino, 2008) and arterial disease (Schnurr et al., 2000) after thirty years. Thus, we expected to find elevated levels of subclinical atherosclerosis among combat veterans. Exposure to extreme psychological trauma may initiate a chronic stress response and a resultant inflammatory, atherosclerotic process (Pollitt et al., 2007; Vidović et al., 2007) and may work through behavioral (e.g., smoking, poor diet, inactivity) (Stellman et al., 2000) or psychological intermediaries (Boscarino, 2008).

Although our primary hypothesis was not supported, this study highlights important factors involved in the study of remote combat exposures. It emphasizes the value of measuring SES in adulthood and childhood, not often both collected in other studies, as military service can change the trajectory of one's socioeconomic position. While non-combat veterans consistently had the highest SES both in childhood and adulthood, combat veterans had higher adult SES but lower childhood SES than non-veterans. This may reflect education received through government subsidies (e.g., G.I. Bill) or the attainment of greater self-efficacy, discipline and skills that are advantageous in future educational and occupational endeavors (Sharp and Krasnesor, 1968; Elder, 1986).

Also, unlike most other studies which focus on a single conflict era, we had data available from multiple eras, allowing us to test for inter-era differences. Combat experiences during conflicts differed considerably, as well as social and political context, conscription rates and socioeconomic composition (Perret, 1990; Appy, 1993). Tests for interaction by era, however, were not significant. Age-adjusted results stratified by era (data not shown) suggest that while World War II and Korean War era combat veterans were more likely to have carotid plaque and increased CIMT than non-combat veterans, associations were weaker or reversed among Vietnam Conflict era veterans, suggesting differences may not yet be manifest in this younger group. However, all confidence intervals were wide and included the null value. Because age and era of service are inherently linked, age-adjustment likely accounted for considerable inter-era variability.

Strengths and limitations

This study provided an opportunity to investigate the long-term association of combat with subclinical atherosclerosis in a large community-based cohort with military and civilian controls. Average follow-up time was long, and participants were of an age where CVD is likely manifest. This study included objective, standardized measures of cardiovascular outcomes, information on specific combat exposures, and a range of physical, behavioral and socioeconomic measures.

Although recalled exposure measurement is not ideal, no other cohort has collected data on combat exposure with long-term follow-up and rigorous cardiovascular outcome measurements. Self-reported combat exposure measurement has precedents (Axelrod et al, 2005; Hoge et al., 2004; Erickson et al., 2001), with reports of high validity and reliability (Janes et al., 1991; Dohrenwend et al., 2007; Stretch and Figley, 1984) and little evidence of falsification of experiences. This scale provides a more specific definition than commonly-used alternatives (e.g., theater *versus* non-theater veterans). We attempted to validate our exposure data; however, this information is not captured in military service or other obtainable records. Other sources (e.g., obituaries, POW lists) were deemed unfeasible, as they are not population based and would not yield appropriate data on a representative sample.

We explored whether a stronger effect was present among those exposed to the heaviest combat. After age-adjustment, effects were modestly increased for CIMT but not plaque among heavy combat veterans (data not shown). However, confidence intervals were wide and overlapped considerably; therefore, heavy and light combat groups were combined.

Although we cannot completely rule out differential CVD mortality in the period between military service and ARIC enrollment, given low CVD mortality rates in young adulthood, bias due to left censoring, if extant, is unlikely to threaten the validity of our findings. Right censoring, however, may be of greater concern, as exposures were assessed 12-14 years after baseline, when 17% of male participants had expired. Male LC-SES participants had slightly better baseline health than the general male ARIC population (data not shown). We took two steps to assess this concern, with methods and assumptions that have been published (Johnson et al., 2010). Briefly, a study on a subset of decedents for whom veteran status was recorded on death certificates found little (2%) excess mortality among veterans, even after adjustment for age, race and education. Also, results from a sensitivity analysis suggest that correcting for even a considerable level of selection bias resulted in minimal change in estimates.

Stress-related psychological conditions (e.g., PTSD) have been associated with increased cardiovascular morbidity and mortality (Boscarino, 2006). While it would have been of interest to provide results stratified on PTSD status, this information was not obtained in the LC-SES interview. As combat exposure is the strongest predictor of PTSD (McFall et al., 1991), and as PTSD would have been assessed as a potential modifier rather than as a confounder, its absence should not detract from our findings (Lee et al, 1995).

In combination, these results do not support the hypothesis that combat exposure is associated with increased long-term risk of subclinical atherosclerosis among men. However, because this study is the first, to our knowledge, to assess the relationship between combat exposure and subclinical atherosclerosis, the long-term effects of combat on cardiovascular health should be examined in other populations, ideally ones that include a representative sample of women and persons of different races and ethnicities.

Acknowledgments

The Atherosclerosis Risk in Communities Study is a collaborative study supported by the National Heart, Lung and Blood Institute contracts R01-HL064142, No.T32-HL07055-27, N01-HC-55015, N01-HC-55016, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, and R21-HL080422-01. We thank the ARIC staff and participants for their important contributions.

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Table 1

Profile of demographic, military and combat background reported by men in the interview (2001-2002), by military and combat history. Life Course Socio-Economic Status, Social Context and Cardiovascular Diseases Study, Atherosclerosis Risk in Communities (ARIC) Study, USA.

	Non-Combat Veterans (REF) [a]	Non-Veterans [a]		Combat Veterans [a]	
		n (%) or mean (std)	p-value [b]	n (%) or mean (std)	p-value [b]
Demographics					
Mean (SD) Age in years at baseline	54.1 (5.1)	51.8 (5.2)	<0.01	57.3 (5.8)	<0.01
n (%) Black	278 (13.1)	643 (31.5)	<0.01	155 (13.2)	0.94
n (%) Father's education < high school	1102 (65.1)	1010 (72.7)	<0.01	634 (69.0)	0.05
n (%) Education < high school	244 (11.5)	625 (30.7)	<0.01	209 (17.8)	<0.01
n (%) Combined family income <$25,000	368 (18.0)	625 (32.5)	<0.01	284 (25.3)	<0.01
n (%) Occupation non-managerial/ professional	1382 (65.0)	1446 (70.9)	<0.01	903 (76.7)	<0.01
Military history					
Mean (SD) Years of service	3.1 (3.2)			4.9 (5.6)	<0.01
Mean (SD) Age in years at induction into service	19.8 (2.4)			19.1 (2.2)	<0.01
Mean (SD) Years elapsed since induction into service	34.3 (5.9)			38.2 (6.8)	<0.01
n (%) Served during World War II era	314 (14.8)			478 (40.6)	<0.01
Korean War era	675 (31.7)			407 (34.6)	
Vietnam Conflict era	506 (23.8)			198 (16.8)	
Combat history					
n (%) Served in combat zone				975 (82.8)	
n (%) Under enemy fire or fired at enemy				700 (59.7)	
n (%) Saw wounded or killed				853 (72.7)	
n (%) Ever wounded or missing				154 (13.1)	

[a] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[b] p-values from Student t-tests for continuous variables and chi-square tests for binary variables.

Table 2

Risk factor profile of male participants at baseline (1987-1989), by military and combat history. Life Course Socio-Economic Status, Social Context and Cardiovascular Diseases Study, Atherosclerosis Risk in Communities (ARIC) Study, USA.

	Non-Combat Veterans (REF) [a]	Non-Veterans [a]		Combat Veterans [a]	
		n (%) or mean (std)	p-value [b]	n (%) or mean (std)	p-value [b]
n (%) Current alcoholic drinking	1492 (70.3)	1212 (59.7)	<0.01	824 (70.3)	0.98
n (%) Heavy alcoholic drinking	228 (10.75)	165 (8.13)	<0.01	124 (10.58)	0.88
n (%) Current cigarette smoking	473 (22.3)	541 (26.5)	<0.01	247 (21.0)	0.40
n (%) Heavy lifetime cigarette smoking	545 (25.9)	438 (21.9)	<0.01	368 (31.7)	<0.01
n (%) Physically inactive	402 (19.0)	516 (25.4)	<0.01	213 (18.2)	0.58
n (%) Prevalent diabetes	167 (7.9)	213 (10.6)	<0.01	123 (10.5)	0.01
n (%) Prevalent coronary heart disease	117 (5.5)	107 (5.2)	0.73	94 (8.0)	0.01
Mean (SD) Pack years of smoking	545 (25.9)	438 (21.9)	<0.01	368 (31.7)	<0.01
Mean (SD) Body mass index (m/kg^2)	27.2 (3.8)	27.8 (4.4)	<0.01	27.7 (4.0)	<0.01
Mean (SD) Waist circumference (cm)	98.4 (10.0)	99.1 (11.6)	0.05	99.6 (10.3)	<0.01
Mean (SD) Systolic blood pressure (mmHg)	119.9 (16.3)	121.8 (17.6)	<0.01	122.5 (16.7)	<0.01
Mean (SD) Total cholesterol (mg/dL)	210.7 (37.9)	209.7 (39.8)	0.42	213.5 (40.4)	0.05
Mean (SD) LDL cholesterol (mg/dL)	139.6 (35.4)	138.3 (37.3)	0.23	141.9 (37.0)	0.01
Mean (SD) HDL cholesterol (mg/dL)	44.2 (13.2)	44.8 (13.5)	0.11	43.7 (12.8)	0.36
Mean (SD) Triglycerides (mg/dL)	140.3 (96.9)	137.0 (84.8)	0.24	148.1 (110.7)	0.04

[a] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[b] p-values from Student t-tests for continuous variables and chi-square tests for binary variables.

Table 3

Observed carotid plaque and intima-media thickness (CIMT) male participants at baseline (1987-1989) and at the second ARIC examination (1990-1992), by military and combat history (N=5347). Life Course Socio-Economic Status, Social Context and Cardiovascular Diseases Study, Atherosclerosis Risk in Communities (ARIC) Study, USA.

	Carotid Plaque [a]	CIMT (μm) [a]
	n (%)[c]	Mean (SD)[c]
Military and combat history [b]		
Non-combat veterans (REF)	970 (48.48)	757.7 (164.1)
Non-veterans	858 (45.09)	745.2 (157.7)
Combat veterans	595 (53.75)	802.4 (182.2)
	RR(95%CI) [c]	RD (95% CI) [c]
Non-veterans		
Unadjusted	0.93 (0.87, 0.99)	-12.48 (-22.32, -2.64)
Adjusted for Age	1.01 (0.94, 1.09)	10.61 (0.81, 20.41)
Adjusted for Age and Race	1.02 (0.96, 1.10)	10.53 (0.55, 20.51)
Adjusted for Age and Childhood Education	0.98 (0.91, 1.06)	6.56 (-4.83, 17.95)
Adjusted for Age, Race and Childhood Education	0.99 (0.92, 1.08)	6.88 (-4.59, 18.35)
Combat veterans		
Unadjusted	1.11 (1.03, 1.19)	44.68 (32.47, 56.89)
Adjusted for Age	0.99 (0.92, 1.07)	12.79 (0.72, 24.86)
Adjusted for Age and Race	0.99 (0.92, 1.07)	12.82 (0.75, 24.89)
Adjusted for Age and Childhood Education	1.01 (0.93, 1.10)	14.56 (1.08, 28.04)
Adjusted for Age and Age at Entry into Service	0.98 (0.91, 1.06)	12.12 (0.05, 24.19)
Adjusted for Age and Duration of Service	1.00 (0.93, 1.08)	11.27 (-1.08, 23.62)
Adjusted for Age, Race, Childhood Education, Age at Entry and Duration of Service	1.01 (0.93, 1.10)	12.18 (-1.64, 26.00)

[a] Carotid plaque is defined as the presence of carotid plaque by B-mode ultrasound at ARIC Visits 1 and/or 2; CIMT is defined as the average far wall imputed CIMT over ARIC Visits 1 and 2.

[b] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[c] n = frequency; % = percentage; SD = standard deviation; RR = risk ratio; RD = risk difference; CI = confidence interval.