



Original Contribution

Posttraumatic Stress Disorder, Combat Exposure, and Carotid Intima-Media Thickness in Male Twins

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Posttraumatic stress disorder (PTSD) is associated with an increased risk of ischemic heart disease, though the pathophysiologic mechanisms remain unclear. Carotid artery intima-media thickness (CIMT) is a measure of subclinical atherosclerosis. We examined whether PTSD and combat exposure were associated with CIMT in Vietnam War-era twins after controlling for shared genetic and childhood factors. Between 2002 and 2010, we studied 465 middle-aged twins from the Vietnam Era Twin Registry who were free from cardiovascular disease. PTSD was diagnosed using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, and CIMT was measured by ultrasound. Mixed-effects regression models were used to examine individual, between-pair, and within-pair associations. Approximately 13% of participants met the criteria for PTSD, and 45% served in the Vietnam Theater. PTSD was associated with 32.7 μm higher CIMT (95% confidence interval (CI): 0.9, 64.5) after adjustment for confounders. The average CIMT for the pair increased by 59.7 μm for each additional twin with PTSD (95% CI: 15.9, 104.2). We found no significant within-pair differences in CIMT when comparing PTSD-discordant co-twins. Results for combat exposure were similar, but its association with CIMT weakened after adjustment for PTSD (95% CI: 7.0, 45.3). Among Vietnam War-era veterans, combat exposure and PTSD are associated with CIMT, though the associations are largely mediated by shared childhood factors.

cardiovascular disease; carotid intima-media thickness; combat exposure; PTSD; twins; Vietnam veterans

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CES, Combat Exposure Scale; CIMT, carotid artery intima-media thickness; CVD, cardiovascular disease; PTSD, posttraumatic stress disorder.

Posttraumatic stress disorder (PTSD) is a psychiatric disorder triggered by exposure to a traumatic event, and it is highly prevalent in combat veterans. The lifetime prevalence of PTSD in the adult US population is approximately 7%, whereas among Vietnam War-era veterans the prevalence is approximately 12%–16% (1, 2). Growing evidence has linked PTSD with an increased risk of cardiovascular disease (CVD), including early-onset heart disease (3, 4) and stroke (5), as well as evidence of myocardial ischemia (6, 7). Proposed mechanisms include abnormal sympathetic activation and hypothalamic-pituitary-adrenal axis dysfunction, but the precise pathways for the increased CVD risk are unknown (8, 9).

Although a connection between PTSD and increased risk of CVD is increasingly being recognized, it remains unclear

whether this increased risk is the result of worsening of the atherosclerotic process or other mechanisms. Carotid artery intima-media thickness (CIMT) is a marker of subclinical atherosclerosis and is predictive of future CVD events (10). A variety of factors, including educational attainment, health behaviors, and depression, may confound the association between PTSD and CIMT. Low educational attainment has been associated with PTSD and CVD (11). PTSD and nicotine dependence appear to share genetic and environmental factors (12). Low levels of physical activity have also been associated with delayed onset of PTSD (13). Depression, a common comorbidity in persons with PTSD, has also been associated with accelerated progression of CIMT. Finally, having served in the Vietnam Theater may also reflect socioeconomic factors,

policies, or other health factors that may influence deployment, especially in families with more than one child, as well as CVD. In addition to traditional CVD risk factors and environmental exposures, genetic factors also influence CIMT (14).

Twin studies are helpful in the determination of causal effects in observational epidemiologic studies. Twin pairs discordant on the exposure of interest provide a useful analog to the counterfactual design for causal inference (15). Twins are matched for age, a key factor in the expression of CVD, and they share familial environments while growing up (e.g., diet and socioeconomic and parental factors) that also contribute to the expression of complex traits such as CVD. These factors are ruled out by comparing twins within pairs. In addition, the study of twins allows parsing the relative contributions of genes and shared/unshared environment to the association of interest. To our knowledge, no studies have assessed the relationship among PTSD, combat exposure, and CIMT in twins.

In a sample of Vietnam War-era twins, we previously reported an association between PTSD and CVD that was independent of shared genetic and familial factors (6). In the present study, we extended this previous research by assessing whether PTSD was associated with CIMT in this same sample. This issue addresses the question of whether plaque burden plays a role in the association between PTSD and CVD. We also examined whether combat exposure is associated with increased CIMT and whether PTSD mediates the association. We examined whether associations persisted after adjustment for potential confounding factors (demographic factors, behavioral factors, depression). Using a co-twin analysis, we then investigated whether associations persisted after controlling for genetic and early familial environmental factors, in addition to cardiovascular risk factors and depression.

METHODS

Study population

The purpose of the Emory Twins Studies was to assess the role of psychological, behavioral, and biological factors in the development of subclinical CVD (16, 17). Participants were middle-aged male twin pairs (monozygotic and dizygotic) who were recruited from the Vietnam Era Twin Registry (18) and were born between 1946 and 1956. The sample included 281 twin pairs; in some pairs, at least 1 member had PTSD or depression, whereas in others, both members were free of PTSD and depression. From this sample of 562 twins, 86 participants with previous CVD (cerebrovascular accident, coronary heart disease, coronary revascularization therapy, or peripheral vascular disease) were excluded. An additional 11 participants for whom we were missing CIMT measurements were excluded (none of whom had PTSD), yielding a final analytic sample of 465 persons.

Twin pairs were examined on the same date at a clinical research facility in the Emory University Hospital. Medical history and data collection occurred during a 24-hour admission under controlled conditions. Anthropometric measurements, blood samples, and behavioral questionnaires for measurement of CVD risk factors were obtained. Zygosity was determined by DNA typing, as previously described

(19). All assessments were completed blindly with respect to PTSD status. The Emory Institutional Review Board approved both study protocols, and informed consent was obtained from all study participants.

Measurement of CIMT

Common CIMT was measured using high-resolution B-mode ultrasonography with standard techniques (20–22). The CIMT was measured on both the near and far walls of the left and right common carotid arteries at the distal end 1.0 cm proximal to the bifurcation. Multiple angles were used to identify the longitudinal image of CIMT showing the maximum CIMT. Measurements were made offline using semiautomated computerized analytical software (Carotid Tools, MIA Inc., Iowa City, Iowa). The average values of maximum CIMT for each of 4 segments (left and right carotid near and far walls) were used as the total mean of maximum CIMT for each twin. Three sonographers measured CIMT over the study period, and all were unaware of the other twin's data. In our laboratory, the mean absolute difference in CIMT measured in 7 subjects who underwent 2 carotid artery examinations performed 3 days apart was 0.03 (standard deviation, 0.02) mm. The mean difference in 2 successive readings of the same 10 segments of common CIMT was 0.02 (standard deviation, 0.02) mm, with a Pearson correlation coefficient of 0.93.

Assessment of PTSD and combat exposure

Lifetime history of PTSD and depression were identified using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (23). Combat exposure was assessed using the Combat Exposure Scale (CES), a 7-item self-report survey that measures stressful wartime experiences (24). The CES score ranges from 0 to 41 and can be classified to reflect 5 categories of increasing combat exposure: none or light (0–8), light-moderate (9–16), moderate (17–24), moderate-heavy (25–32), and heavy (33–41) (25). The combat exposure score was dichotomized for ease of interpretation as combat exposure (more than none or light exposure) versus none or light exposure.

Assessment of potential confounding and mediating factors

We collected information on demographic characteristics (age and educational attainment), behavioral factors (smoking and physical activity level), cardiovascular risk factors (body mass index, mean systolic blood pressure (SBP), lipid profile, diabetes), and depression. Physical activity level was measured using the Baecke Questionnaire of Habitual Physical Activity used in the Atherosclerosis Risk in Communities (ARIC) Study (26). A trained research nurse obtained information about medication usage. Diabetes was defined as a blood glucose level of 126 mg/dL or higher or treatment with insulin or oral antihyperglycemic medications. Direct high-density lipoprotein was measured using homogeneous assays (Equal Diagnostics, Exton, Pennsylvania). Body mass

index was calculated as weight in kilograms divided by height in meters squared.

Potential confounders of the association between PTSD and CIMT included demographic factors (age, educational level), behavioral factors, depression, and ultrasound observer. Age and ultrasound observer were included as potential confounders because they differed by combat exposure and PTSD status. Cardiovascular risk factors were considered to be mediators of the association between PTSD and CIMT. In analyses of the association between combat exposure and CIMT, only age and high school educational attainment were considered potential confounders, whereas PTSD was considered a mediator.

Statistical analysis

All analyses used mixed regression models with a random intercept for each twin pair to account for correlations between brothers (27). PROC MIXED and PROC GENMOD in SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina), were used for continuous and categorical outcome variables, respectively. Analyses of the associations of PTSD with combat exposure and with CIMT were sequentially adjusted for potential confounders and then potential mediators. We also included an indicator variable for the observer who

measured CIMT in individual analyses. Combat exposure was analyzed as a dichotomous variable (none or light versus more than none or light).

In the initial analyses, twins were considered individually. Subsequent analyses evaluated the associations of combat exposure and lifetime PTSD with CIMT, both between and within twin pairs. The individual-level analysis compared individual twins with different levels of exposure while treating them as though they were unrelated, whereas the between-pair analysis compared twin pairs with different levels of pairwise exposure, that is, none, only one, or both twins with the exposure. Unlike the individual-level analysis, the between-pair analysis quantified familial influences in the association because some family characteristics could be related to both PTSD and subclinical atherosclerosis. In within-pair analyses, co-twins in each pair were compared. Within-pair analyses also controlled for shared unmeasured familial and early life environmental factors. When within-pair estimates are smaller than the estimates obtained when twins are analyzed separately, it suggests confounding by factors shared by twin pairs. Assessment of within-pair associations can also evaluate potential genetic confounding, such as a shared genetic basis for thickening of the carotid artery wall and PTSD. Among twins who are discordant for the exposure, if the within-pair association is smaller for monozygotic twins

Table 1. Twin Characteristics by History of PTSD, Emory Twins Study, 2002–2010

Characteristic	Total No. of Subjects	No PTSD (n = 405)		PTSD (n = 60)	
		%	Mean (SD)	%	Mean (SD)
Demographic factors					
Age, years	465		55.1 (3.1)		57.1 (2.2)
Did not complete high school	465	27.9		30.0	
Behavioral factors					
No. of alcoholic drinks per week	463		4.6 (8.3)		7.9 (12.8)
Baecke score	462		7.4 (1.7)		7.3 (2.0)
Smoking status					
Current smoker	465	21.7		36.7	
Past smoker	464	41.9		35.0	
Never smoker	464	36.4		28.3	
Cardiovascular factors					
Systolic blood pressure	465		129.7 (15.6)		132.7 (15.4)
HDL cholesterol	465		40.2 (22.2)		40.4 (11.8)
Diabetes	465	9.6		10.0	
Hypertension	465	33.7		43.3	
Body mass index ^a	464		29.3 (4.8)		29.8 (4.8)
Psychiatric comorbidity					
History of depression	463	20.6		56.7	
Military service					
Combat exposure score ^b	465		0 (5)		16.0 (9.5)
In Vietnam Theater	465	39.0		91.0	

Abbreviations: HDL, high-density lipoprotein; PTSD, posttraumatic stress disorder; SD, standard deviation.

^a Weight (kg)/height (m)².

^b Values are expressed as median (interquartile range).

than for dizygotic twins, genetic confounding is possible (15). To determine whether the potential effect of exposures on CIMT was different within monozygotic and dizygotic twin pairs, we tested for interaction between the within-pair association and zygosity. Tests of statistical significance were 2-sided, with $\alpha = 0.05$.

RESULTS

Overall, 12.9% of twins met the criteria for a lifetime history of PTSD. Twins with a history of PTSD were an average of 2 years older, but there was no significant difference in other demographic factors (Table 1). There was no difference in cardiovascular risk factors. Twins with PTSD were more likely to be smokers and to have a history of depression. Overall, 45% of twins served in the Vietnam Theater, and 55% of participants reported no combat exposure. When CES was categorized, 79% ($n = 369$) reported no or light combat exposure, 12% ($n = 53$) reported light-moderate exposure, 7% ($n = 33$) reported moderate exposure, and 2% ($n = 10$) reported moderate-heavy combat exposure. Among those who served in Vietnam, the corresponding proportions of combat exposure were 54% ($n = 141$), 25% ($n = 64$), 16%

($n = 41$), and 4% ($n = 11$). Twins with a lifetime history of PTSD were more likely to have served in the Vietnam Theater, and they had higher median CES scores than did their PTSD-free counterparts. There were 148 twin pairs who were concordant for combat exposure and 60 twin pairs who were discordant. Of those concordant for combat exposure, 139 twin pairs were unexposed and 9 pairs were exposed. There were 165 twin pairs who were concordant for PTSD status and 38 twin pairs who were discordant. Among the 165 twin pairs who were concordant for PTSD, 158 pairs were free from PTSD and 7 pairs had PTSD.

PTSD and CIMT

The overall mean CIMT was 750 (standard deviation, 110) μm . In analyses in which twins were treated as individuals, there was a statistically significant unadjusted association between PTSD and CIMT (Table 1), with a lifetime history of PTSD being associated with an average 35.3 μm higher CIMT (95% CI: 6.9, 63.8; $P = 0.015$). In the final model that was adjusted for all potential confounding factors, a lifetime history of PTSD continued to be significantly associated with higher CIMT, which was on average 32.7 μm (95% CI:

Table 2. Sequential Models for the Association Between Carotid Artery Intima-Media Thickness and Posttraumatic Stress Disorder, Emory Twins Study, 2002–2010

Model	Total No. ^a	Individuals			Between Pairs			Within Pair		
		Effect Estimate, μm	95% CI	P Value ^b	Effect Estimate, μm	95% CI	P Value ^b	Effect Estimate, μm	95% CI	P Value ^b
Unadjusted	465	35.3	6.9, 63.8	0.015	76.5	33.4, 119.7	<0.001	6.7	-29.6, 42.9	0.717
Adjusted for potential confounders ^c										
Demographic factors ^d	465	21.9	6.9, 50.1	0.135	51.5	7.3, 95.6	0.023	7.4	-28.8, 43.5	0.689
Served in the Vietnam Theater	465	27.8	3.1, 58.8	0.078	53.8	9.4, 98.1	0.018	14.5	-24.7, 53.6	0.468
Health behaviors ^e	461	23.1	-7.6, 53.8	0.140	49.5	5.5, 93.5	0.028	8.2	-30.7, 47.0	0.679
Depression	459	32.7	0.9, 64.5	0.044	59.7	15.9, 104.2	0.009	16.8	-23.3, 56.9	0.409
Adjusted for potential mediators										
CVD risk factors ^f	459	23.5	-5.2, 55.6	0.112	47.0	4.2, 58.3	0.032	18.9	-20.5, 58.3	0.346

Abbreviations: CI, confidence interval; CVD, cardiovascular disease.

^a Number of individuals.

^b The effect estimates and P values were obtained from mixed linear regression including a random intercept for the pair. All adjusted models included zygosity, and individual analyses included a variable indicating the sonographer. The effect estimates express the difference in carotid artery intima-media thickness associated with posttraumatic stress disorder. Between-pair analysis estimates reflect the mean pairwise difference in carotid artery intima-media thickness for each additional twin with a diagnosis of posttraumatic stress disorder. Within-pair analysis estimates reflect the difference in carotid artery intima-media thickness comparing twins with posttraumatic stress disorder with their brothers who do not have posttraumatic stress disorder.

^c Each model was adjusted for the variable listed and the ones above.

^d Age and whether he completed high school.

^e Smoking status and physical activity level.

^f Diabetes, mean systolic blood pressure, mean high-density lipoprotein cholesterol level, and body mass index.

Table 3. Sequential Models for the Association Between Carotid Artery Intima-Media Thickness and Combat Exposure, Emory Twins Study, 2002–2010

Model	Total No. ^a	Individuals			Between-Pair			Within-Pair		
		Effect Estimate, μm	95% CI	<i>P</i> Value ^b	Effect Estimate, μm	95% CI	<i>P</i> Value ^b	Effect Estimate, μm	95% CI	<i>P</i> Value ^b
Unadjusted	465	27.9	4.8, 51.0	0.018	54.7	15.7, 93.7	0.006	18.7	–10.23, 47.6	0.205
Adjusted for demographic factors ^c	465	23.2	0.2, 46.3	0.048	33.8	–5.4, 73.0	0.091	18.0	–10.9, 46.9	0.22
Additionally adjusted for PTSD	465	19.2	–7.0, 45.3	0.151	28.8	–11.6, 69.2	0.162	11.9	–20.0, 43.7	0.46

Abbreviation: CI, confidence interval.

^a Number of individuals.

^b The effect estimates and *P* values were obtained from mixed linear regression including a random intercept for the pair. All adjusted models included zygosity, and individual analyses included a variable indicating the sonographer. The effect estimates express the difference in carotid artery intima-media thickness associated with more than none or light combat exposure. For between-pair analyses, these estimates reflect the mean pairwise difference in carotid artery intima-media thickness (in μm) for each additional exposed twin in the pair. For within-pair analyses, these estimates reflect the difference in carotid artery intima-media thickness comparing twins with more than none or light combat exposure with their brother with none or light significant combat exposure.

^c Age and whether he completed high school.

0.9, 64.5; *P* = 0.044) higher in twins with PTSD than in those without PTSD. Including cardiovascular risk factors, which are potential mediators, in the model weakened the association, with a 9- μm decrease in the effect estimate (β = 23.5; 95% CI: –5.2, 55.6; *P* = 0.112).

When the overall association was separated into between- and within-pair components, a significant association was found between but not within twin pairs. The between-pair analysis showed that the CIMT pair average was 76.5 μm larger for each incremental twin with PTSD in the pair (from none to one to both twins with PTSD; *P* < 0.001). The association was diminished after adjustment for confounding factors (β = 59.7; 95% CI: 15.9, 104.2; *P* = 0.009). Additional adjustment for cardiovascular risk factors resulted in a 12.7- μm reduction in the regression coefficient, but the association remained statistically significant (95% CI: 4.2, 58.3; *P* = 0.032). In contrast, there was no association between PTSD and CIMT in within-pair analyses (Table 2). There was also no statistical interaction between zygosity and the within-pair association of PTSD and CIMT (*P* = 0.85). Within-pair mean differences in the association of PTSD with CIMT in zygosity-stratified models were similar and did not suggest genetic confounding (for dizygotic twins, mean difference = 13.8 μm , 95% CI: –60.2, 87.8; *P* = 0.710; for monozygotic twins, mean difference = 17.3 μm , 95% CI: –23.78, 58.3; *P* = 0.406).

Combat exposure and CIMT

Of the persons with PTSD, 62% reported having some degree of combat exposure, and 91% of those subjects served in the Vietnam Theater. Of persons without PTSD, 36% reported having combat exposure, and 39% of those subjects served in the Vietnam Theater. In individual analyses, there was a statistically significant unadjusted association between CES and CIMT, such that light-moderate or more combat

exposure was associated with a 27.9- μm (95% CI: 4.8, 51.0; *P* = 0.018) increase in CIMT (Table 3). The association was slightly weakened after adjustment for age and high school completion but remained statistically significant (23.2 μm , 95% CI: 0.2, 46.3; *P* = 0.048). After controlling for a history of PTSD, the association was attenuated and no longer statistically significant. Similar to what was found in the PTSD analyses, there was a significant between-pair association but no within-pair association between CES and CIMT (Table 3).

DISCUSSION

In the present study of middle-aged male Vietnam War–era veterans, a lifetime history of PTSD and combat exposure were both positively associated with CIMT in individual analyses after controlling for multiple covariates. However, because no significant associations were found in within-pair analyses, it appears that familial factors confounded these relationships. Because there was no evidence of interaction between zygosity and the within-pair effect, familial factors rather than genetic factors appear to be implicated. Our results do not support a causal association between PTSD or combat exposure and CIMT; rather, they suggest that parental or shared environmental factors play an important role in the relationship.

Because PTSD in veteran populations is largely a result of combat exposure, we examined whether combat exposure itself was associated with CIMT and whether PTSD may mediate such an association. Indeed, we found a statistically significant association between combat exposure and CIMT in individual comparisons but not in within-pair analyses. Again, familial factors appeared to confound this relationship, because there was no significant difference in within-pair comparisons. Combat exposure was no longer an independent predictor of CIMT once PTSD was included in the model in individual analyses, which suggests that the familial

influences on combat exposure and CIMT occur in part through influencing vulnerability to PTSD.

To our knowledge, our study is the first to examine the association of PTSD and combat exposure with CIMT in twin pairs. Although no previous studies have examined the association between PTSD and CIMT, other studies have examined various sources of chronic stress, with mixed results. Our individual-level analysis results are consistent with data that linked high occupational psychosocial stress with increased CIMT (28–30). On the other hand, an analysis of the ARIC Study population did not find a difference in CIMT by comparing nonveterans, noncombat veterans, and combat veterans (31). Depression has been shown to be associated with CIMT in some studies (32, 33) but not others (34). Psychological strain was not found to be associated with CIMT in a community study, although it was associated with carotid plaque (35). None of these previous studies had the ability to control for familial, environmental, or genetic factors as we did in this twin study. Differences in results may be due to different methods of CIMT measurement; although CIMT was measured as a mean of far wall carotid thickness values in the ARIC Study, our study measured the mean of the maximum CIMT from the near and far walls.

The results of individual analyses in this study are also consistent with investigations that have found a positive association between PTSD and clinical cardiovascular events. PTSD among Vietnam War veterans has been linked to early heart disease death (3) and a higher risk of incident CVD, even after controlling for depression (4). An association of PTSD with clinical coronary heart disease events, as well as with measures of myocardial perfusion indicators of ischemic heart disease, was also found in our twin population, independent of familial factors (6). However, there was no association between PTSD and atherosclerotic risk factors such as hypertension and dyslipidemia, which have been implicated in the accumulation of atherosclerotic plaque. Overall, evidence of an association between PTSD and traditional cardiometabolic risk factors remains inconsistent (36–38). Thus, it is possible that other mechanisms are involved. For example, PTSD and combat exposure have been associated with decreased heart rate variability, an indicator of autonomic dysfunction that may increase cardiovascular risk through abnormalities in cardiac rhythm and other mechanisms related to neurocardiac regulation (39). PTSD has also been associated with molecular biomarkers of endothelial function and inflammation, both in the steady state and after reminders of the trauma, which suggests that immune and vascular mechanisms other than the atherosclerotic process may be implicated as triggers of acute coronary syndromes in PTSD (40–42).

The results of this twin study point to a potential nongenetic familial component in the relationship between PTSD and CIMT. PTSD may be, in part, a marker for exposures related to both PTSD and atherosclerotic vascular disease. For example, children exposed to unfavorable socioeconomic status are known to be at increased risk for both PTSD (43, 44) and the development of clinical and subclinical CVD later in life (45–47). Other adverse childhood experiences, including exposure to abuse and family dysfunction (e.g., domestic violence, substance abuse, or incarceration of a family member),

have been related to trauma exposure in adulthood and PTSD (47, 48) and have also shown a graded dose-response relationship with many adult diseases, including CVD (49). Even exposure to less severe but still at-risk family psychosocial environments, such as cold, unaffectionate interactions, conflict, aggressive interpersonal behavior, and neglect, has been associated with a small increase in CIMT (50, 51). Hypothalamic-pituitary-adrenal axis dysregulation or epigenetic modifications have been proposed as biological mechanisms that mediate the association between childhood factors and adult PTSD (52); these same factors could potentially increase the risk of atherosclerotic vascular disease. An advantage of our study is that childhood socioeconomic status and family dysfunction are shared by twin pairs and are accounted for by design in within-pair comparisons. Once these familial factors were controlled for in within-pair analyses, no association was found between either PTSD or combat exposure and CIMT, which suggests that familial factors may explain these associations.

Health behaviors, such as smoking and physical activity, share a complex relationship with PTSD. Persons with PTSD are more likely to smoke, which contributes to carotid atherosclerosis. This suggests that smoking may partially mediate the association between PTSD and CIMT (12). However, evidence also suggests that smoking soon after a disaster predicts delayed-onset PTSD symptoms (13). Furthermore, a twin analysis using members of the Vietnam Era Twin Registry suggested that the associations between PTSD and nicotine dependence were explained in part by shared genetic and environmental factors (53). Therefore, in the present study, smoking was considered to be a potential confounder, as was physical activity, which has also been inversely associated with delayed-onset PTSD (54). The potential for health behaviors to act as both confounders and mediators suggests that they would best be considered as time-varying covariates. Unfortunately, health behaviors were only measured once, precluding their use as time-varying covariates.

There are several limitations to the present study. The cross-sectional design of the study limited our ability to assess the temporal association between combat exposure, PTSD, and CIMT. For instance, PTSD was assessed as lifetime PTSD according to the standard psychiatric diagnosis from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. In addition, some covariates, such as smoking, may be time-varying confounders, a fact that limits inferences that could be made. On the other hand, it is unlikely that a subclinical indicator such as CIMT can affect the likelihood of being exposed to combat or developing PTSD. Second, lack of subjects with extreme combat exposure may have resulted in an underestimation of the association between combat exposure and CIMT. Because study participants were middle-aged male veterans, the findings of this study cannot be readily generalized to women or to persons of different ages. Finally, residual confounding due to unmeasured factors is possible. However, the twin design has the advantage of capturing unmeasured familial and early environmental confounding factors, which is not possible with traditional observational designs.

Among Vietnam War-era veterans, PTSD and combat exposure are both associated with CIMT. However, utilizing the

methodologic strength of a twin study design, we found that these associations appear to be mediated by shared familial or other early environmental factors. Adverse characteristics of early environments may play a role in the increased risk of subclinical atherosclerotic vascular disease associated with combat exposure and PTSD. Future research should elucidate the specific early environmental factors involved in the relationship between combat, PTSD, and subclinical atherosclerotic vascular disease. If a causal relationship exists between PTSD and CIMT, this is likely mediated by multiple mechanisms, including early environmental factors.

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