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ORIGINAL ARTICLE

Longitudinal associations between post-traumatic stress disorder and metabolic syndrome severity

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Background. Post-traumatic stress disorder (PTSD) is associated with elevated risk for metabolic syndrome (MetS). However, the direction of this association is not yet established, as most prior studies employed cross-sectional designs. The primary goal of this study was to evaluate bidirectional associations between PTSD and MetS using a longitudinal design.

Method. A total of 1355 male and female veterans of the conflicts in Iraq and Afghanistan underwent PTSD diagnostic assessments and their biometric profiles pertaining to MetS were extracted from the electronic medical record at two time points (spanning ~2.5 years, $n = 971$ at time 2).

Results. The prevalence of MetS among veterans with PTSD was just under 40% at both time points and was significantly greater than that for veterans without PTSD; the prevalence of MetS among those with PTSD was also elevated relative to age-matched population estimates. Cross-lagged panel models revealed that PTSD severity predicted subsequent increases in MetS severity ($\beta = 0.08$, $p = 0.002$), after controlling for initial MetS severity, but MetS did not predict later PTSD symptoms. Logistic regression results suggested that for every 10 PTSD symptoms endorsed at time 1, the odds of a subsequent MetS diagnosis increased by 56%.

Conclusions. Results highlight the substantial cardiometabolic concerns of young veterans with PTSD and raise the possibility that PTSD may predispose individuals to accelerated aging, in part, manifested clinically as MetS. This demonstrates the need to identify those with PTSD at greatest risk for MetS and to develop interventions that improve both conditions.

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Key words: Accelerated aging, cross-lagged design, longitudinal, metabolic syndrome, PTSD, veterans.

Introduction

Post-traumatic stress disorder (PTSD) is associated with substantial medical morbidity (Schnurr *et al.* 2000; Ahmadi *et al.* 2011; Bartoli *et al.* 2013; O'Donovan *et al.* 2015), with striking effects observed for obesity (Bartoli *et al.* 2015), and cardiometabolic and cardiovascular conditions (Ahmadi *et al.* 2011; Heppner *et al.* 2012; Bartoli *et al.* 2013; Wentworth *et al.*, 2013; Roberts *et al.* 2015; Rosenbaum *et al.* 2015*b*; Roy *et al.* 2015; Sumner *et al.* 2015). The co-occurrence of PTSD with metabolic syndrome (MetS), as defined by three or more of central obesity, hypertension, dyslipidemia, and elevated blood sugars [National Cholesterol Education Program (NCEP), 2001; Grundy *et al.* 2005], is particularly high, with recent meta-analyses suggesting that MetS is prevalent in nearly 40% of those with PTSD (Bartoli *et al.* 2013; Rosenbaum *et al.* 2015*b*). The association between PTSD and MetS is intriguing given that stress is implicated in the pathogenesis and course of MetS (Vitaliano *et al.* 2002; see also Epel, 2009) and that MetS may be part of the pathway linking PTSD to subsequent deleterious health conditions, such as cardiovascular disease (Roy *et al.* 2015; Sumner *et al.* 2015), type 2 diabetes (Roberts *et al.* 2015), decreased

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cortical thickness (Wolf *et al.* in press), cognitive impairment (Green *et al.* 2016), and premature mortality (Ahmadi *et al.* 2011).

Although nearly all of the studies linking PTSD to MetS employed a cross-sectional design, many investigators hypothesize that the stress of PTSD influences MetS risk (e.g. Bartoli *et al.* 2013). This could occur through biological pathways, such as increased autonomic reactivity, immune and hypothalamic-pituitary-adrenal (HPA) axis system dysregulation (Kibler *et al.* 2014; Levine *et al.* 2014), and/or oxidative stress processes (Grattagliano *et al.* 2008). Potential PTSD-related behavioral pathways include poor nutrition and sedentary lifestyle (Hall *et al.* 2015), cigarette and alcohol use (Dennis *et al.* 2014), and poor sleep (Talbot *et al.* 2015). It is also possible that MetS may negatively affect PTSD symptoms. For example, greater pre-deployment inflammation (C-reactive protein), which often co-occurs with MetS, was recently shown to predict subsequent post-deployment PTSD (Eraly *et al.* 2014). PTSD and MetS may also exert bidirectional effects on the severity of each other, particularly in trauma-exposed samples. In support of this, bidirectional effects have been reported for depression and MetS (Pulkki-Råback *et al.* 2009), and this may generalize to PTSD given that PTSD is highly comorbid with depression (Pietrzak *et al.* 2012) and both disorders may arise out of a shared underlying vulnerability towards internalizing psychopathology (Miller *et al.* 2008). Only longitudinal designs can address the question of directionality. To our knowledge, two such studies exist to date, and both had analytic concerns that limited the strength of the causal conclusions.

Specifically, Francis *et al.* (2015) followed 78 physically abused children and 349 non-abused children into middle age and found that childhood abuse was associated with PTSD symptoms during young adulthood, which, in turn, predicted obesity in middle age. Baseline obesity was not controlled for analytically, making it difficult to draw conclusions about the direction of this association. Farr *et al.* (2015) also suggested that PTSD was associated with increasing metabolic risk by showing that, among 55 urban-area community adults, greater PTSD severity was associated with increased obesity and systolic blood pressure over the course of 2.5 years, controlling for baseline body mass index (BMI). Unfortunately, results were difficult to interpret because of the small sample size, control for only baseline BMI, and the fact that PTSD symptoms were split into quartiles based on sample distribution (i.e. not evaluated per the DSM diagnostic definition or total severity). Neither study tested whether MetS predicted subsequent PTSD.

In light of these concerns, our aim was to evaluate potential bidirectional influences between PTSD and MetS using a cross-lagged panel model (Rosenthal & Rosnow, 1991), which simultaneously evaluates the longitudinal effect of each variable on the other while controlling for baseline levels of both PTSD and MetS. We hypothesized that PTSD would be associated with increasing MetS risk over time, and that if there was evidence for MetS influencing subsequent PTSD, that this effect would be weaker in magnitude than that for PTSD predicting MetS. This aim was evaluated in a large national cohort of US military veterans deployed to the wars in Iraq and/or Afghanistan and who completed two waves of assessments, separated by approximately 2.5 years (see Rosen *et al.* 2012). As women were oversampled and represented just over 50% of the cohort, we were also able to evaluate potential sex differences in the relationship between PTSD and MetS.

Method

Participants

Participants were U.S. Army or Marine Corps veterans enrolled between 2009 and 2012 in the baseline assessment of Project VALOR (Veterans' After-Discharge Longitudinal Registry), a registry of VA mental healthcare users with and without PTSD who deployed in support of Operation Enduring Freedom or Operation Iraqi Freedom (see Supplementary material and Rosen *et al.* 2012 for details). To be included veterans must have undergone a mental health evaluation at a VA facility. Veterans with probable PTSD according to VA medical records (i.e. at least two instances of a PTSD diagnosis by a mental health professional associated with two separate visits) were oversampled at a 3:1 ratio, and female veterans were oversampled to comprise ~50% of the cohort.

The current study included the largest possible subsample of $n = 1355$ participants from Project VALOR (out of 1649 total) who had data pertaining to, at least, time 1 (T1) PTSD severity and T1 MetS severity. Demographic characteristics of this sample are shown in Table 1. Time 2 (T2) PTSD severity was available for $n = 1124$ (83%) of the T1 sample and T2 MetS severity data were available for $n = 971$ (72%) of the T1 participants, yielding the final T2 total of 971 (see Supplementary material for comparisons of those with *v.* without T2 data).

Measures

PTSD module of the Structured Clinical Interview for DSM

Doctoral-level diagnosticians assessed current (past month) PTSD via telephone using the PTSD module of the Structured Clinical Interview for DSM (SCID). The SCID for DSM-IV (First *et al.* 2000) was

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Table 1. *Demographic and PTSD-related characteristics of the sample*

Variable	Mean (S.D.)	Range	*n*	%
Age (years)	37.86 (9.96)	22–69		
Sex				
Male			655	48.3
Female			700	51.7
Race/ethnicity				
White			878	64.8
Black			224	16.5
Hispanic			174	12.8
Other			70	5.2
Missing			9	0.7
Education level				
High school degree or equivalent			136	10.0
Some post-high school education			760	56.1
College degree or higher			454	33.5
PTSD				
Dx at T1			902	66.6
Dx at T2			664	68.4
Severity at T1	9.99 (4.79)	0–17		
Severity at T2	11.87 (4.97)	0–20		

T1, Time 1; T2, time 2; PTSD, post-traumatic stress disorder; Dx, diagnosis; S.D., standard deviation.

Demographic characteristics are based on T1 data ($n = 1355$). The sample size at T2 was 971 and T2 PTSD percentages are based on that total. Comparisons of demographic and other differences between those with and without T2 data are presented in the Supplementary material. PTSD severity is based on a symptom count of the number of endorsed items on the SCID PTSD module.

administered at T1 and for DSM-5 (First *et al.* 2015) at T2. Both have demonstrated excellent psychometric properties (Bovin & Weathers, 2012; Regier *et al.* 2013). The SCID was administered up to two times at each time point in relation to two, distinct index traumatic experiences. *PTSD symptom severity* was operationalized as the maximum score (number of PTSD symptoms endorsed) from either of the two SCID administrations at each time point. *PTSD diagnosis* was operationalized as meeting the DSM-IV (at T1)/DSM-5 (at T2) diagnostic criteria based on either of the two concurrent SCID administrations. Interviews were digitally recorded and 100 were randomly chosen for secondary independent ratings at T1 and T2 yielding excellent inter-rater agreement at T1 ($\kappa = 0.91$) and T2 ($\kappa = 0.82$).

Life events checklist for DSM-IV (LEC)

The LEC (Gray *et al.* 2004) is a self-report questionnaire of trauma exposure that comprises the PTSD Criterion A1 assessment on the Clinician Administered PTSD Scale (Blake *et al.* 1995). Participants indicated if they experienced, witnessed, learned about, or were exposed to any of 16 potentially traumatic events.

Additional measures that were the focus of secondary analyses are described in the Supplementary material.

Procedure

At T1, participants provided informed consent verbally over the telephone in accordance with the research protocol approved by all institutional review boards and the Human Research Protection Office of the US Army Medical Research and Materiel Command. Study staff then invited participants to complete a self-administered survey either online or via mail. Once completed, participants underwent diagnostic interview by telephone and received $50 compensation. Approximately 2–4 years later, participants were re-contacted for the second phase of the study, which followed the same approach as T1. Participants were compensated $100 at T2.

Data pertaining to MetS features were extracted from the VA electronic medical record using laboratory values that were linked as closely as possible in time to the SCID-based PTSD assessment and were no more than ±6 months of the PTSD assessment. On average,

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Table 2. *Metabolic syndrome criteria definitions*

Criterion	Definition	
Central obesity	BMI ⩾25[a]	
Dyslipidemia		
HDL (mg/dl)	<40 (men) <50 (women)	Or taking cholesterol-lowering medication
Triglycerides (mg/dl)	⩾150	Or taking medication for elevated triglycerides
Elevated blood sugars		
Fasting glucose (mg/dl)	⩾100	Or taking medication for diabetes or elevated glucose
Hypertension		
Systolic blood pressure (mmHg)	⩾130	Or taking medication for hypertension
Diastolic blood pressure (mmHg)	⩾85	

BMI, Body mass index; HDL, high-density lipoprotein.

Three out of five criteria (central obesity, low HDL, high triglycerides elevated glucose, and elevated systolic or diastolic blood pressure) were required for the metabolic syndrome diagnosis.

[a] See note 1.

there was well less than a month between the PTSD/biometric assessments (see Supplementary materials). The two PTSD assessments occurred, on average, ~2.5 years apart (range 18.80–56.50 months; see Supplementary material). Time difference variables were evaluated as covariates in preliminary analyses.

MetS was defined per the NCEP Adult Treatment Panel (ATP) III definition (NCEP, 2001; Grundy *et al.* 2006), as detailed in Table 2[1]†. *MetS severity* was defined as the number of MetS criteria present (0–5). *MetS diagnosis* was defined as meeting three or more of the MetS criteria (NCEP, 2001; Grundy *et al.* 2006).

Data analysis

We first examined the prevalence[2] of PTSD diagnosis (on the SCID) and MetS diagnosis (and each MetS criterion) at each time point in the sample overall and then conducted χ^2 analyses to evaluate MetS-related differences as a function of PTSD diagnosis at each time point. We also compared a population-based estimate of MetS among 20- to 39-year-olds (20.3%; Ervin, 2009) with the T1 MetS prevalence among veterans with PTSD in this same age group using a *Z* test for two population proportions. We then examined each dimensional MetS variable (raw laboratory values and criteria count) as a function of PTSD diagnosis using *t* tests for independent samples. We tested potential differences in metabolic profiles as a function of PTSD diagnosis and sex (and their interaction) using multivariate analysis of variance (MANOVA). Correlations between total lifetime trauma exposure, PTSD severity, and MetS severity at and across each time point and those between MetS, PTSD severity, and potential covariates were evaluated (see Supplementary material).

We then ran our primary cross-lagged panel model using the statistical modeling program Mplus 7.11 (Muthén & Muthén, 2012). In the path model, the autoregressive effects of each variable on itself over time (e.g. T1 PTSD to T2 PTSD) were modeled, as were the cross-lagged paths (e.g. T1 PTSD to T2 MetS). These models focused on PTSD severity (symptom count on the SCID) and MetS severity (number of MetS criteria met). The concurrent correlation between the two variables at T1 was modeled as was their residual correlation at T2. Total lifetime trauma exposure (on the LEC) was included as a predictor of T1 MetS and PTSD severity and the indirect effects of trauma exposure on T2 PTSD and MetS severity via T1 PTSD and MetS severity were estimated using the 'model indirect' command. Significant covariates, based on the results of initial bivariate correlations, were included as predictors of T1 PTSD and MetS severity. The model employed the robust maximum likelihood estimator, which accounts for non-normality in the data by adjusting the standard errors to reduce the likelihood of Type I error. This estimator includes all available data using full information likelihood estimation, conditional on the presence of at least one exogenous variable. Due to missing covariate data, the final sample size for the cross-lagged model was 1341. Path models were evaluated using standard fit indices and guidelines (Hu & Bentler, 1999).

We then conducted a logistic regression in SPSS v. 21 (IBM Corp., USA) to test whether T1 PTSD severity predicted T2 MetS diagnosis, controlling for T1 MetS

† The notes appear after the main text.

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severity and demographic covariates. Analyses evaluating potential moderators, covariates, and confounders (including combat exposure, depression, substance use, and psychotropic medication use) of our main associations are detailed in the Supplementary material.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Prevalence and severity of PTSD, MetS, and their co-occurrence

Descriptive statistics pertaining to the presence and severity of current PTSD at T1 and T2 are listed in Table 1 and descriptive statistics for MetS are shown in Table 3. Among veterans with PTSD aged <40 years at T1, the prevalence of MetS was 29.0%, which was significantly greater than the 20.3% previously reported (Ervin, 2009) in an age-matched epidemiological sample ($Z = -3.19$, $p = 0.001$). In contrast, the prevalence of MetS among veterans without current PTSD in this age group (20.2%) was nearly identical to that reported by Ervin (2009). In the full sample, the mean number of T1 MetS criteria was 2.00 (Table 3), with 89.4% meeting at least one MetS criterion and 70.0% meeting at least 2 MetS criteria. At T2, the mean number of MetS criteria was 2.10 (Table 3), with 90.5% above the threshold for at least one MetS criterion and 63.6% above the threshold for at least two criteria.[3] At T1, 17.4% were taking cholesterol-lowering medication, 27% anti-hypertensive medication, and 2.4% were taking diabetes-related medication. At T2, 15.1% were taking cholesterol-lowering medication, 23.6% were taking anti-hypertensive, and 3.2% were taking diabetes-related medications. This medication use was factored into the MetS definition (Table 2).

As shown in Table 3, χ^2 analyses revealed that the prevalence of T1 MetS diagnosis was greater among those with a concurrent PTSD diagnosis (36.6%) compared to those without (26.3%, $p < 0.001$). This held at T2, wherein the prevalence of T2 MetS diagnosis was 37.8% among those with a concurrent PTSD diagnosis and 30.9% among those without ($p = 0.038$). Individuals with PTSD at T1 also met criteria for a greater number of T1 MetS features compared to those without T1 PTSD (Table 3). χ^2 analyses suggested that a greater percentage of individuals with T1 PTSD met the criteria for central obesity, hypertension, elevated blood sugars, and high triglycerides than those without PTSD (Table 3). Additionally, t tests revealed higher mean raw laboratory values for each T1 MetS component among this group (Table 3). Those with PTSD at T2 also met criteria for a greater number of T2 MetS features compared with those without T2 PTSD (Table 3); however, no group differences emerged in the mean T2 raw metabolic values and the only T2 criterion difference was for hypertension (Table 3).

MANOVAs examined sex, PTSD, and sex × PTSD differences in raw metabolic laboratory values at each time point. At T1, the multivariate test yielded main effects for sex (Pillai's trace = 0.163, $F_{6,800} = 25.96$, $p < 0.001$) and PTSD (Pillai's trace = 0.030, $F_{6,800} = 4.14$, $p < 0.001$), but no significant interaction between the two (Pillai's trace = 0.013, $F_{6,800} = 1.78$, $p = 0.10$). All sex differences were in the direction of women evidencing less pathological laboratory values than the men (details available from first author). The main effect of sex held at T2 (Pillai's trace = 0.158, $F_{6,619} = 19.35$, $p < 0.001$), but there were no significant multivariate main effects of T2 PTSD or of PTSD × sex. Based on this, sex was not included as a moderator in primary models, though it was included as a covariate and evaluated further in secondary analyses (see Supplementary material).

Cross-lagged panel models

Preliminary correlation-based analyses are detailed in the Supplementary material and Supplementary Table S1. We found that none of the time difference variables were correlated with their respective dependent variables, so they were excluded from path models. In contrast, race, sex, age, and education were associated with some or all of the PTSD and MetS variables (detailed in the Supplementary material) and were therefore included as covariates of T1 PTSD and MetS.[4]

The cross-lagged panel model fit the data well: $\chi^2(10, n = 1341) = 59.10$, $p < 0.001$, root mean square error of approximation = 0.06, standardized root mean square residual = 0.02, confirmatory fit index = 0.97, Tucker–Lewis index = 0.91. As shown in Fig. 1, T1 PTSD severity was a strong predictor of T2 PTSD severity ($\beta = 0.67$, $p < 0.001$), and T1 MetS severity was strongly related to T2 MetS severity ($\beta = 0.62$, $p < 0.001$). After controlling for these autoregressive effects, we found a significant cross-lagged effect, such that T1 PTSD severity predicted T2 MetS severity ($\beta = 0.08$, $p = 0.002$), but T1 MetS did not predict T2 PTSD severity ($\beta = 0.005$, $p = 0.82$). The association between PTSD and MetS severity at T1 was significant; however, their residual correlation was not significant at T2 after controlling for the shared effects of T1 variables. Age, sex, and education were significant covariates of T1 MetS severity;

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Table 3. *Metabolic syndrome diagnosis and features in the overall sample and as a function of PTSD diagnosis*

	Mean (S.D.)								% Meeting MetS criterion							
	All		PTSD+		PTSD-		*p*		All		PTSD+		PTSD−		*p*	
MetS variable	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
Obesity (BMI, kg/m^2)	29.78 (5.41)	30.22 (5.69)	30.03 (5.29)	30.13 (5.58)	29.28 (5.60)	30.40 (5.92)	0.018	0.509	79.9	81.8	82.5	80.8	74.7	83.9	0.001	0.254
Blood pressure (mmHg)									50.6	53.6	56.1	57.7	39.6	44.6	0.000	0.000
Diastolic	76.22 (10.37)	77.42 (10.07)	76.83 (10.36)	77.41 (10.03)	75.02 (10.32)	77.43 (10.16)	0.003	0.973								
Systolic	122.14 (12.77)	123.26 (13.68)	122.76 (12.94)	123.44 (13.84)	120.92 (12.37)	122.87 (13.34)	0.013	0.555								
HDL cholesterol (mg/dl)	47.71 (15.08)	49.99 (15.71)	46.76 (15.08)	49.91 (15.62)	49.54 (14.93)	50.16 (15.96)	0.009	0.849	46.1	41.6	47.3	43.2	43.8	38.0	0.316	0.208
Triglycerides (mg/dl)	143.67 (107.16)	147.29 (105.16)	152.04 (115.51)	151.20 (114.42)	127.18 (86.28)	138.59 (80.41)	0.001	0.155	48.0	51.8	50.6	51.8	43.0	51.9	0.029	0.985
Glucose (mg/dl)	95.61 (19.23)	98.15 (28.13)	97.38 (21.34)	98.40 (25.53)	91.91 (13.09)	97.57 (33.46)	0.000	0.708	13.0	16.6	14.7	17.5	9.5	14.4	0.020	0.287
Total no. MetS features	2.00 (1.26)	2.10 (1.28)	2.11 (1.27)	2.16 (1.30)	1.77 (1.21)	1.96 (1.24)	0.000	0.026								
MetS Dx									33.1	35.6	36.6	37.8	26.3	30.9	0.000	0.038

MetS, Metabolic syndrome; S.D., standard deviation; PTSD+, positive post-traumatic stress disorder diagnosis; PTSD−, negative post-traumatic stress disorder diagnosis; T1, time 1; T2, time 2; BMI, body mass index; HDL, high-density lipoprotein; Dx, diagnosis. *p* values for dimensional variables are based on independent *t* tests as a function of current (T1 or T2) PTSD diagnosis. *p* values for categorical variables are based on Pearson χ^2 tests.

The number of participants for each analysis varied due to missing data. Details are as follows: At time 1: (*a*) BMI total = 1303, PTSD+ = 864, PTSD− = 439; (*b*) diastolic BP total = 1325, PTSD+ = 881, PTSD− = 444; (*c*) systolic BP total = 1326, PTSD+ = 882, PTSD− = 444; (*d*) HDL cholesterol total = 900, PTSD+ = 594, PTSD− = 306; (*e*) triglycerides total = 888, PTSD+ = 589, PTSD− = 299; (*f*) glucose total = 1013, PTSD+ = 686, PTSD− = 327; (*g*) total no. of MetS features total = 1355, PTSD+ = 741, PTSD− = 407; (*h*) Mets Dx total = 1355, PTSD+ = 741, PTSD− = 407. Sample sizes at time 2: (*a*) total = 927, PTSD+ = 635, PTSD− = 292; (*b*) total = 944, PTSD+ = 649, PTSD− = 295; (*c*) total = 946, PTSD + 649, PTSD− = 297; (*d*) total = 669, PTSD+ = 461, PTSD− = 208; (*e*) total = 658, PTSD+ = 454, PTSD− = 204; (*f*) total = 760, PTSD+ = 532, PTSD− = 228; (*g*) total = 971, PTSD+ = 664, PTSD− = 307; (*h*) total = 971, PTSD+ = 664, PTSD− = 307. Using the higher BMI cut-point of 30 in the diagnostic algorithm yielded a MetS prevalence of 25.7% at T1 and 28.5% at T2 (of those with T2 data). A greater percentage of individuals with PTSD were diagnosed with MetS using this more stringent BMI criterion at both T1 and T2, per χ^2 analysis. Using the higher BMI cut-point of 30 in the MetS criteria count revealed that 79% were above the threshold for at least 1 MetS criterion and 49% were above the threshold for at least 2 MetS criteria at T1. At T2, 80% were above the threshold on at least 1 MetS criterion and 52% were above the threshold on at least 2 MetS criteria. At both time points, *t* tests revealed that individuals with PTSD met the threshold for a greater number of MetS criteria than did those without PTSD.

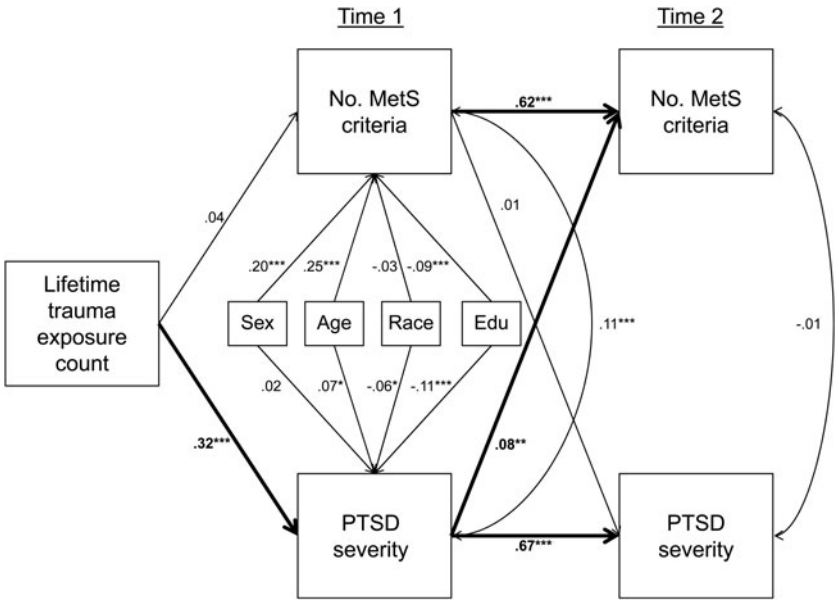

Fig. 1. The figure shows the results of the cross-lagged panel model. Primary and significant paths of interest are bolded. Correlations are represented via double-headed arrows and regressive paths via single-headed arrows. MetS, Metabolic syndrome; PTSD, post-traumatic stress disorder; Edu, educational attainment. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

age, race, and education were significant covariates of T1 PTSD severity (Fig. 1). Total lifetime trauma exposure at T1 was significantly associated with T1 PTSD severity but not with T1 MetS. Results suggested indirect effects of trauma on T2 MetS severity via T1 PTSD severity ($\beta = 0.03$, $p = 0.002$) and on T2 PTSD severity via T1 PTSD severity ($\beta = 0.21$, $p < 0.001$). In total, the model explained 40% of the variance in T2 MetS severity and 44% of the variance in T2 PTSD severity. Analyses of potential confounds of key associations are reported in the Supplementary material; none altered the primary pattern of results.

Effects of PTSD on subsequent MetS diagnosis

Finally, to evaluate the effects of PTSD severity on subsequent MetS diagnosis, we conducted a logistic regression with T1 PTSD severity and T1 MetS severity as predictors of T2 MetS diagnosis, controlling for age, race, sex, and education. We found that for every additional PTSD symptom at T1, the odds ratio (OR) for MetS diagnosis at T2 increased by 5.6% [95% confidence interval (CI) 1.9–9.4%, Wald $\chi^2(1, n = 961) = 9.09$, $p = 0.003$]. This means that for every 10 symptoms endorsed on the SCID at T1, the odds of a MetS diagnosis at T2 increased by 56%. Each increase in MetS criteria at T1 was associated with nearly three times the odds for a subsequent MetS diagnosis [OR 2.86, 95% CI 2.44–3.37, Wald $\chi^2(1, n = 961) = 124.31$, $p < 0.001$]. Nagelkerke's R^2 for the overall model was 0.40 ($p < 0.001$).[5]

Discussion

This study adds to a growing chorus of concerns regarding substantial PTSD-related metabolic health decline among veterans of the conflicts in Iraq and Afghanistan. In contrast to prior epidemiological estimates of MetS in the US population (20.3% among 20- to 39-year-olds; Ervin, 2009), we found substantially more veterans (29.0%) with PTSD in this age range with MetS. Our estimates of the prevalence of MetS (36.6% at T1 and 37.8% at T2) among those with PTSD are remarkably similar to the near 40% that has been reported in two recent meta-analyses (Bartoli *et al.* 2013; Rosenbaum *et al.* 2015*b*). This study extended prior work by addressing a critical question that has, to date, gone unanswered regarding the temporal relationships between PTSD and MetS. Results indicated that PTSD increased MetS risk over the course of, on average, 2.5 years, after controlling for initial MetS features, but that MetS did not predict subsequent PTSD symptoms.

That PTSD longitudinally predicted MetS carries implications for conceptualizing the course and treatment of both conditions. MetS is considered a syndrome (as opposed to a disease) in part because there is no obvious biological process that connects the individual MetS features. Traumatic stress may be one pathogenic environmental factor that, through biological and behavioral pathways, simultaneously intensifies the degeneration of multiple physiological processes and links them together. For example, PTSD may lead to both cardiovascular and HPA axis

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system dysregulation (Kibler *et al.* 2014; Brudey *et al.* 2015), which would be expected to increase blood pressure, circulating lipids, blood sugars, and inflammation (Epel, 2009); together, these alterations can increase central fat deposits (Epel, 2009). At the same time, PTSD-related increases in reactive oxygen species (Miller & Sadeh, 2014; Gautam *et al.* 2015; Atli *et al.* in press) may alter the expression of genes important for regulating metabolic processes, ultimately compounding metabolic dysregulation (Grattagliano *et al.* 2008). In addition, PTSD-related poor sleep (Gavrieli *et al.* 2015; Talbot *et al.* 2015), unhealthy diet (Hall *et al.* 2015), insufficient exercise (Georgiades *et al.* 2000; Hall *et al.* 2015), cigarette and alcohol use (Dennis *et al.* 2014), and psychotropic medication use (Vancampfort *et al.* 2015) may exert effects on metabolic health that additively and/or synergistically further contribute to the cascade of broad metabolic dysfunction.

We suspect that PTSD-related MetS may reflect an underlying process wherein the stress and chronicity of PTSD symptoms contribute to accelerated cellular aging and premature disease onset (Miller & Sadeh, 2014; Lohr *et al.* 2015; Wolf *et al.* 2016). The prevalence of MetS is strongly associated with age in the US population (Ervin, 2009); however, we found that PTSD was associated with MetS independent of age, with a prevalence that was greater than expected by age. Thus, MetS may occur prematurely among those with PTSD and may be a clinical manifestation of accelerated aging. Consistent with this, prior work suggests that: (*a*) PTSD is related to advanced cellular age compared to chronological age, as reflected in DNA methylation (Wolf *et al.* 2016) and telomere length (Tyrka *et al.* 2016); and (*b*) metabolic dysregulation is also associated with shortened telomere length (Epel, 2009) and contributes to biological aging (Belsky *et al.* 2015). Moreover, in our prior work in an independent sample of veterans from the wars in Iraq and Afghanistan, we found that PTSD-related MetS was cross-sectionally associated with substantial and widespread decreases in cortical thickness across temporal, parietal, and frontal brain regions (Wolf *et al.* in press). Together, these findings suggest that PTSD-related accelerated cellular aging may be reflected in premature genomic, physical health, and neurocognitive decline, highlighting the need to identify those at greatest risk and develop effective interventions.

It may be prudent to closely monitor the metabolic profiles of individuals with PTSD, even among young adults, so that early indications of problems can be discussed with the patient, careful consideration paid to the potential for weight gain side effects in prescribed medications, lifestyle changes recommended, and an appropriate treatment plan aimed at reducing metabolic pathologies enacted. Early screening for other age-dependent health conditions (e.g. cardiovascular disease, type 2 diabetes) may also be warranted. Although we found sex-related differences in MetS features, we found no evidence that PTSD was differentially related to MetS as a function of sex; thus early MetS screening among individuals with PTSD should be conducted with both men and women.

With respect to treatment implications, a recent, if small, meta-analysis found that physical activity was an effective intervention for PTSD (Rosenbaum *et al.* 2015*c*) and may also improve physical health parameters among individuals with PTSD (Rosenbaum *et al.* 2015*a*). No study to date has evaluated if exercise intervention for PTSD can reverse MetS, making this an important area for future research. It is also important for future trials of PTSD treatments to evaluate if psychological interventions for PTSD have indirect beneficial effects on MetS.

Results should be interpreted in light of study limitations including that metabolic profiles were not directly measured but instead were extracted from the medical record. This undoubtedly added methodological variance to the measurement of MetS (e.g. time between assessments, laboratory procedures), which would be expected to attenuate the magnitude of our associations. This medical record approach also led to missing data that we addressed via our analytic design, but which may alter results compared with complete data. There are also a number of other potentially important covariates and health indicators (e.g. insulin, inflammation, waist-to-hip-ratio, waist circumference) that we were unable to reliably assess via medical record review and that could have allowed us to test the International Diabetes Federation's ethnicity-based MetS criteria (Alberti *et al.* 2005). With respect to the longitudinal design of the study, we controlled for baseline PTSD symptoms, but the metabolic profiles of individuals prior to trauma exposure and PTSD onset were not available. We did not observe PTSD group differences in raw laboratory values at T2 and this may have been due to differences in sample characteristics (e.g. PTSD severity; see Supplementary material) among those who did *v.* did not complete T2. The DSM changed from version IV to 5 between T1 and T2, and this could have also lead to different patterns of results in group-based analyses at T2 compared to T1. However, this would not be expected to substantively alter our primary results, which were focused on PTSD severity evaluated via regression, as prior work comparing DSM-IV with DSM-5 PTSD *severity* suggests very strong correlations across the two definitions (Miller *et al.* 2013; Bovin *et al.* in press).

The strengths of this study include that it is the first longitudinal evaluation of potential bi-directional

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associations between PTSD and MetS that controls for baseline effects and does so parsimoniously in a single analysis. Additional study strengths include the large sample size, inclusion of Iraq/Afghanistan veterans from across the country, the ability to evaluate sex-specific effects, and our use of a structured diagnostic interview to assess PTSD.

In conclusion, we found that young veterans of the conflicts in Iraq and Afghanistan with PTSD exhibited signs of substantial premature health decline. This should be of grave concern to mental health and primary-care clinicians alike and suggests the critical importance of developing interventions that reduce both psychiatric and metabolic pathology. MetS is hugely costly on its own (Sullivan *et al.* 2007), and the economic, personal, and societal costs can only balloon if the condition gives rise to other associated diseases such as premature cardiovascular disease (Lakka *et al.* 2002), type 2 diabetes (Wilson *et al.* 2005), cancer (Esposito *et al.* 2012), dementia (Yaffe *et al.* 2004), and death (Lakka *et al.* 2002). This is a major public health concern and addressing it in this population now has the potential to reduce preventable morbidity and mortality among the nation's newest cohort of veterans.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291716000817.

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Declaration of Interest

None.

Notes

[1] Waist-to-hip ratio and waist circumference are superior metrics of central obesity but were not available in the medical record, so we used BMI instead. A BMI cut-off of 25 is classified as 'overweight' and a BMI of 30 is the cut-point for 'obese' (WHO, 2000), with a wide range of optimal cut-points for metabolic syndrome reported in the literature (e.g. Zandieh *et al.* 2012; Liu *et al.* 2013). Given this, we ran our primary cross-lagged analyses using both cut-points and found no differences in results (i.e. same pattern of statistical significance and cross-lagged path coefficients within 0.01 of each other). Thus, we retained the lower cut-point to be as inclusive as possible.

[2] We use the term 'prevalence' throughout the manuscript with the following caveat: as the registry over-sampled veterans with probable PTSD and also over-sampled women, prevalence may be over-estimated and may not generalize to the broader population of veterans of the wars in Iraq and Afghanistan.

[3] See note to Table 3 for discussion of results using the higher BMI cut-point.

[4] In a separate model, we also included these demographic variables as covariates of T2 MetS and PTSD severity and found that doing so did not alter the primary pattern of results. Therefore, for the sake of simplicity, we present the results with these variables included as covariates of the T1 variables only.

[5] Similar results were obtained when we substituted T1 PTSD diagnosis for T1 PTSD severity: the odds of a subsequent MetS diagnosis increased by 75% for veterans with T1 PTSD (95% CI 1.24–2.46, $p = 0.001$).

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