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The underlying mechanisms by which PTSD symptoms are associated with cardiovascular heath in male UK military personnel: The ADVANCE cohort study

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ABSTRACT

Post-Traumatic Stress Disorder (PTSD) has been identified as an independent risk factor for cardiovascular disease, but the mechanisms of this relationship are not well understood. This study investigates the associations between PTSD symptom clusters (hyperarousal, intrusive thoughts, avoidance behaviours and emotional numbing) and mechanisms of cardiovascular disease including cardiometabolic effects, inflammation, and haemodynamic functioning. In the ADVANCE study cohort of UK male military personnel, 1111 participants were assessed for PTSD via questionnaire and cardiovascular risk via venous blood sampling, pulse wave analysis and dual energy x-ray absorptiometry between 2015 and 2020. Variable selection procedures were conducted to assess which of the symptom clusters if any were associated with cardiovascular risk outcomes. Associations were confirmed via robust regression modelling. Avoidance behaviours were associated with greater systolic Blood Pressure (BP) (Adjusted Coefficient (AC) 0.640 (95% Confidence Interval (CI) 0.065, 1.149). Emotional numbing was associated with greater estimated glucose disposal rate (AC -0.021 (95%CI -0.036, −0.005). Hyperarousal was associated with greater levels of (log)triglycerides (exponentiated-AC 1.009 (95%CI 1.002, 1.017). Intrusive thoughts were associated with greater visceral adipose tissue (AC 0.574 (95%CI 0.020, 1.250). Nonlinear relationships were observed between emotional numbing with heart rate and intrusive thoughts with systolic BP. Limited evidence is present for symptom associations with lipoproteins and pulse wave velocity. No associations were observed between PTSD symptom clusters and high sensitivity c-reactive protein, diastolic BP, total cholesterol, or haemoglobin fasting glucose. In conclusion, symptom clusters of PTSD were associated with increased cardiovascular risk via cardiometabolic and haemodynamic functioning mechanisms, but not inflammation.

Abbreviations: BPM, Beats per minute; CI, Confidence Interval; CVD, Cardiovascular Disease; HPA, Hypopituitary Adrenal Axis; HsCRP, High sensitivity C-Reactive Protein; IQR, Interquartile range; PCL, Posttraumatic stress disorder clinical checklist; PTSD, Post-Traumatic Stress Disorder; SAS, Sympathetic Adrenal System.

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1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a stress-related disorder and possible consequence of trauma, such as exposure to warzones and/or experiencing physical trauma (Forbes et al., 2012; Stevelink et al., 2018). PTSD is characterised by symptoms such as intrusive thoughts, avoidance behaviours, emotional numbing and hyperarousal (Asmundson et al., 2000). Intrusive thoughts symptoms include repeated, disturbing thoughts or dreams of the traumatic event, as well as physical reactions (e.g. heart pounding, trouble breathing) when reminded of the traumatic event. Avoidance behaviours include active avoidance of thoughts, discussion, activities and situations linked to the traumatic event. Emotional numbing symptoms include anhedonia, memory problems, and feeling distant to friends/loved ones. Hyperarousal symptoms includes reporting problems with sleep, difficulty concentrating, increased startle response and irritability/angry outbursts. It is important to note that PTSD is a heterogenous disorder, and symptom severity of these clusters vary in presentation.

PTSD has been linked to lifestyle factors such as increased smoking, poorer diet, and decreased physical exercise (Dyball et al., 2019; van den Berk-Clark et al., 2018a). These lifestyle factors, in turn, affect cardiovascular functioning. PTSD has also been linked to neurological changes, including changes to the Hypopituitary Adrenal Axis (HPA) and Sympathetic Adrenal System (SAS). These changes cause autonomic dysregulation, leading to alteration in responses from the sympathetic and parasympathetic nervous system (Brudey et al., 2015). It is through these alterations that PTSD has also been linked to poor physical health outcomes, including Cardiovascular Disease (CVD) (Pacella et al., 2013). US military personnel with PTSD who deployed to the Iraq/Afghanistan conflicts have been observed to have increased CVD risk, despite the group still being of relatively young age (pooled mean age 30 years) (Dyball et al., 2019). Whilst associations between PTSD and CVD have been confirmed in the scientific literature, questions remain as to the specific biological and psychological mechanisms by which PTSD affects CVD (Koenen et al., 2017). Hyperarousal symptoms are theorised to be primarily responsible for alterations in the nervous system (Brudey et al., 2015; Presciutti et al., 2020), though few studies have investigated links between symptom clusters and CVD risk (Pérez et al., 2012). Proposed biological mechanisms include increased inflammation, cardiometabolic effects, and changes to haemodynamic functioning (Edmondson and Cohen, 2013; Levine et al., 2014; Schneider and Schwerdtfeger, 2020).

Inflammation is a process by which the immune system reacts to determined threats of bodily health. This process has previously been found to be associated with stress, whereby continued exposure to stress dysregulates the immune system and produces chronic, low-grade inflammation (Edmondson and Cohen, 2013). High sensitivity C-Reactive Protein (HsCRP) is one inflammatory marker which, in chronically elevated levels, has been shown to linked to CVD, though the evidence for a relationship between HsCRP and PTSD is mixed (Dyball et al., 2019; Renna et al., 2018).

Cardiometabolic effects include components of the metabolic syndrome, such as increased presence of glycated haemoglobin ($HbA1_C$; e.g. fasted blood glucose), increased Diastolic Blood Pressure (DBP), increased Systolic Blood Pressure (SBP), increased presence of body fat, increased levels of triglycerides, increased levels of Low-Density Lipoproteins (LDL), known as 'bad' cholesterol, as well as decreased levels of High-Density Lipoproteins (HDL), known as 'good' cholesterol. Each of these individual components of metabolic syndrome have been associated with CVD (Von Känel et al., 2010; Wiklund et al., 2008). PTSD has been shown to be linked to an increased risk of experiencing the metabolic syndrome as well as all singular aspects of the metabolic syndrome (Levine et al., 2014). There is however, uncertainty in the direction and magnitude of the association between PTSD and SBP (Sumner et al., 2021).

Haemodynamic functioning refers to the dynamic flow of blood through the circulatory system. Haemodynamic functioning is heavily regulated by homeostatic mechanisms, such as through the HPA and SAS. Aspects of haemodynamic functioning include resting heart rate and arterial stiffness. Resting heart rate has been found to be higher in those with PTSD (Schneider and Schwerdtfeger, 2020). Increased arterial stiffness is a recognised surrogate of large artery atherosclerosis and reduced compliance. Arterial stiffness leads to increased left ventricular afterload and a rise in central BP. Increased arterial stiffness is associated with a wide range of adverse cardiovascular outcomes including stroke and cardiovascular death. The measurement of pulse wave velocity (PWV) is the gold-standard non-invasive marker of arterial stiffness, with stiffer arteries leading to increased PWV. Arterial stiffness has been found to be higher in those with PTSD (Tomlinson and Cockcroft, 2011).

Assessment of whether PTSD symptoms are associated with inflammation, cardiometabolic effects or haemodynamic functioning would greatly help with the understanding of the underlying mechanisms by which PTSD affects CVD. However, assessment of similar, highly correlated symptom clusters is difficult. Interpretation of the effects of independent variables on the dependent variable can change distinctly depending on the variables included in the model, and falsely including/excluding independent variables can bias models. Assessment of model stability though Bootstrap Inclusion Frequencies (BIF) allows us to quantify how likely a variable is pertinent to the model of interest and whether pairs of independent variables correlated to one another are competing for selection through co-dependence (De Bin and Sauerbrei, 2018; Heinze et al., 2018; Sauerbrei et al., 2020). A second step including model averaging is suggested as a method of addressing model uncertainty (Heinze et al., 2018). State of the art variable selection procedures are becoming more popular in the literature, though still lag behind other, less reliable methods of variable selection (such as stepwise regression modelling) (Heinze et al., 2018; Sauerbrei et al., 2020).

Recently, an investigation of the mental health outcomes of the ADVANCE study cohort, a cohort of combat-injured UK military personnel and a frequency-matched uninjured comparison group, found that 17.2% of the injured group and 10.7% of the uninjured group reported probable PTSD (Dyball et al., 2022). Along with measures of mental well-being, the ADVANCE study cohort completed a comprehensive health suite of assessments including cardiovascular health (Boos et al., 2021).

1.1. Aims

The aim of this study is to examine whether PTSD symptom clusters are associated with cardiovascular risk factors including inflammation, cardiometabolic effects and haemodynamic functioning, in the ADVANCE study cohort. We will also assess the relative importance of these symptom clusters via variable selection procedures and confirm results via robust regression models. We hypothesise that severity of symptoms within the symptom cluster hyperarousal will be selected as the most important symptom cluster and be associated with a worse cardiovascular risk profile.

2. Methods

2.1. Study design and participants

The ADVANCE study is a cohort study investigating the long-term effects of sustaining a physical combat injury on physical and psychosocial well-being (Bennett et al., 2020). 579 physically injured UK male military personnel and 566 uninjured personnel frequency-matched to the injured group on sex, age, rank, regiment, role on deployment, service and deployment era were recruited from a sample provided by the Ministry of Defence, Defence Statistics (UK) (Bennett et al., 2020). Eligibility criteria for the injured group included having sustained a physical combat injury during a deployment to Afghanistan; having an aeromedical evacuation due to the injury which resulted in admission to

a UK hospital; and no history of cardiovascular, liver, or renal disease before injury. Eligibility criteria for the uninjured group included having deployed to Afghanistan and sustaining no physical combat injuries; and no history of cardiovascular, liver, or renal disease prior to deployment. This study is secondary data analysis and cross-sectional, using data from the baseline visit of the ADVANCE study participants.

2.2. Procedure

Participants were invited to a study day at the UK Defence Medical Rehabilitation Centre Headley Court (2015–2018) or Stanford Hall (2018–2020). Participants took part in a comprehensive set of health tests including clinical assessments, a research nurse-led clinical interview and self-report questionnaires. Prior to the study visit, participants were asked to fast and refrain from caffeine or alcohol from midnight of the day of the appointment (approximately 8 h prior to venous blood sampling and Vicorder assessment).

2.3. Ethics

The ADVANCE study has approval from the Ministry of Defence Research Ethics Committee (MODREC; protocol No:357/PPE/12). All participants gave written informed consent and investigation was carried out in accordance with the 2013 version of the declaration of Helsinki.

2.4. Materials

2.4.1. Exposure

Post-traumatic stress disorder (PTSD)

PTSD was measured using the PTSD Clinical Checklist (PCL-C), a 17-item measure of PTSD (Blanchard et al., 1996). Scores range from 17 to 83. Probable PTSD was defined as a score ≥50, a cut off with good diagnostic accuracy in military populations (Karstoft et al., 2014). The four factor solution based on the DSM-IV criteria was used (Asmundson et al., 2000): Hyperarousal (n = 5 items; score 5–25), avoidance behaviours (n = 2 items; score 2–10), emotional numbing (n = 5 items; score 5–25) and intrusive thoughts (n = 5 items; score 5–25). Higher scores reflect greater symptom severity. Cronbach's alpha for this measure was 0.96, with subscale scores ranging from 0.81 (avoidance behaviours) to 0.92 (intrusive thoughts).

2.4.2. Outcome

Inflammation

High sensitivity C-reactive protein (HsCRP)

HsCRP was measured from venous blood sampling and assayed at local hospital laboratories. HsCRP was measured in mg/l, with a lower detection limit of 0.10 mg/l.

Haemodynamic functioning

Vicorder assessment

PWV, blood pressure and resting heart rate were assessed using a Vicorder (Skidmore Medical, UK). Measurements were taken from participants in the supine position at a 30-degree angle after a rest period of 5 min by trained research nurses in a temperature-controlled environment, three times. The mean score of the three readings taken for resting heart rate (measured in beats per minute (bpm)) and brachial SBP and DBP (measured in millimetres of mercury (mmHg)) were taken during pulse wave analysis readings from the cuff of the upper arm. The mean score of the three PWV measurements (measured in metres per second (m/s)) were taken from readings from the cuff at the upper arm and neck. Following recommended guidance (Van Bortel et al., 2012), if PWV readings differed from one another by 0.5 m/s or greater, the median value was taken. Similarly, for resting heart rate, DBP and SBP, the median was taken if readings differed by 2.5x the median absolute deviation (Leys et al., 2013). If all three readings differed by greater than 2.5x the median absolute deviation from one another, the observation was removed from analysis (excluded observations range from 15 for resting heart rate to 53 for PWV).

Cardiometabolic effects

Blood glucose and insulin resistance

$HbA1_C$ were assayed from venous blood samples and reported/measured in mmol/mol. $HbA1_C$ was converted to $HbA1_C$% using the International Federation of Clinical Chemistry-National Glycohemoglobin Standardisation Program equation for the purposes of estimating insulin resistance (Hoelzel et al., 2004). Estimated Glucose Disposal Rate (eGDR) was used as an indicator of insulin resistance as previously described (Boos et al., 2021). This was calculated as: eGDR mg/kg/minute = 21.158-(0.09 x abdominal waist circumference [cm]) - (3.407 x hypertension [yes = 1, no = 0]) - (0.551 x $HbA1_C$%). Hypertension was defined as current hypertensive medication use or current hypertension defined as SBP (≥140 mmHg) and DBP (≥90 mmHg). eGDR is measured in milligrams per kilogram per minute (mg/kg/min). Lower eGDR is reflective of greater relative insulin resistance.

Dyslipidaemia

Blood serum and plasma samples were taken from participants in a fasted state. Samples were analysed at a local NHS laboratory and assessed for levels of triglycerides, total cholesterol, HDL and LDL. Levels were taken in mmol/l. For the purposes of this study bloods were transformed into mg/dl to increase interpretability of results (Rugge et al., 2012).

Obesity

Whole body fat was assessed using Dual-Energy X-ray Absorptiometry (DEXA, Vertec Horizon Discovery, UK) during a whole-body scan. Participants were laid in a supine position with the neck and spine aligned to the centre of the DEXA table. Legs were apart and feet turned inwards. Visceral adipose tissue area was measured in cm^2.

2.4.3. Confounders

Age at assessment

Age in years at time of ADVANCE assessment was used.

Combat injury

Details of combat injury were collected from electronic medical records, information provided by Ministry of Defence Statistics (Health) department and supplemented by participant self-report during the nurse-led clinical interview. Combat injury was coded as 0 (uninjured) or 1 (injured) (Boos et al., 2021).

Medication

Participants' self-reported current medication use during the clinical interview. Medications were coded using the Anatomical Therapeutic Chemical Classification Index 2020 (WHO Collaboration Centre for Drug Statistics Methodology, 2020). Medications of interest for the current study included medications that affected cardiovascular or mental health: agents acting on the renin-angiotensin system; antihypertensives; calcium channel blockers; corticosteroids for systemic use; diuretics; drugs used in diabetes; immunosuppressants; lipid modifying agents; anabolic agents for systemic use; anti-gout preparations;

psychoanaleptics (drugs that produce a calming mental health effect) and psycholeptics (drugs that provide a stimulating mental health effect). Medication use was coded as 0 (not on medication of interest) and 1 (on medication of interest).

Socioeconomic status

Rank at sampling was used as an indicator of socioeconomic status; junior non-commissioned officer rank (NATO OR2-OR4), senior non-commissioned officer rank (NATO OR5-OR9) and commissioned officer rank (NATO OF1-OF6) (Yoong et al., 1999).

2.5. Data analysis

Data analysis was conducted using the statistical software package STATA 17.0. Henceforth the term 'confounders' refers to the a-priori chosen variables: age at assessment, combat injury, current medication-use and socioeconomic status (Alvares et al., 2016; Boos et al., 2021, de Mestral and Stringhini, 2017; North and Sinclair, 2012). In line with best practice, spearman's correlations were calculated between all variables of interest (Heinze et al., 2018; Sauerbrei et al., 2020). Moderate correlations were defined as correlations $\geq$0.4 and $<$ 0.7, and strong correlations were defined as $\geq$0.7. Classification of normal clinical ranges for each outcome can be found in supplementary materials 1. Symptom clusters were assessed as part of this analysis regardless of probable PTSD status (PCL score $\geq$50).

Multivariable normality was investigated by completing linear regression on each of the cardiovascular risk outcomes including all PTSD symptom cluster scores and confounders in the model. PTSD symptom clusters were centred (e.g. PTSD symptom cluster score-mean PTSD symptom cluster score) prior to inclusion in the model to address multicollinearity between symptom clusters. Linear regression diagnostics were conducted at this stage, assessing residual normality, Cook's D, leverage, heteroscedasticity and variance inflation factor. Variables were considered for transformation if residual normality was not achieved. Triglycerides and HsCRP achieved multivariable normality after log-transformation. Coefficients for log-transformed outcome models were exponentiated and presented based on the percentage change in geometric mean values. Residual outliers were defined as Cook's D $> 4/n$, where n is the sample size. Presence of residual outliers ranged from 7.0% ($HbA1_C$) to 14.3% (PWV). Additionally during regression diagnostics, PTSD symptom clusters were assessed for non-linear relationships with the dependent variable based on visual inspection of the augmented component plus residual plot (Lanius et al., 2006). Symptom clusters with potential non-linear relationships were transformed into restricted cubic splines with three knots. Univariable regression was conducted to compare the linear and non-linear models and non-linear models were confirmed via a likelihood ratio test ($p <$ 0.05).

Variable selection procedures

Variable selection procedures were conducted to assess whether PTSD symptom clusters were associated with each CVD risk outcome after controlling for confounders based on recommendations from the current literature (Heinze et al., 2018; Sauerbrei et al., 2020) (Fig. 1). First, a screening step was undertaken using all symptom clusters in a bootstrap-resampling procedure that produces Bootstrap Inclusion Frequencies (BIF), generated using the 'mfpboot' program in STATA. Linear relationships were assessed with 1 degree of freedom. Non-linear relationships were assessed using the in-built tool for non-linear assessment with no limit on degrees of freedom. Models were assessed using 1000 bootstrap replications. Due to the presence of residual outliers, steps were repeated excluding outliers. Symptom clusters with bootstrap inclusion frequencies of $\geq$30% were assessed for co-dependence via $\chi 2$ of the 2 $\times$ 2 inclusion frequency tables, then, if assessed as independent, went on to the second step (De Bin and Sauerbrei, 2018). No co-dependency issues were noted and so no strategy was implemented to address co-dependence (see supplementary materials 3). Bootstrapped Weighted Absolute Least Squares (WALS) model averaging was implemented at this stage with symptom clusters selected from the screening step with 1000 replications. Variables with a t-score $>$1 or $<$ -1 and standard error bands that did not cross 0 were selected. For non-linear relationships, the restricted cubic spline function was used at this stage. If multiple symptom clusters were selected for a single outcome, assessment of whether models including multiple symptom clusters or singular symptom clusters were assess via likelihood ratio test ($p <$ 0.05).

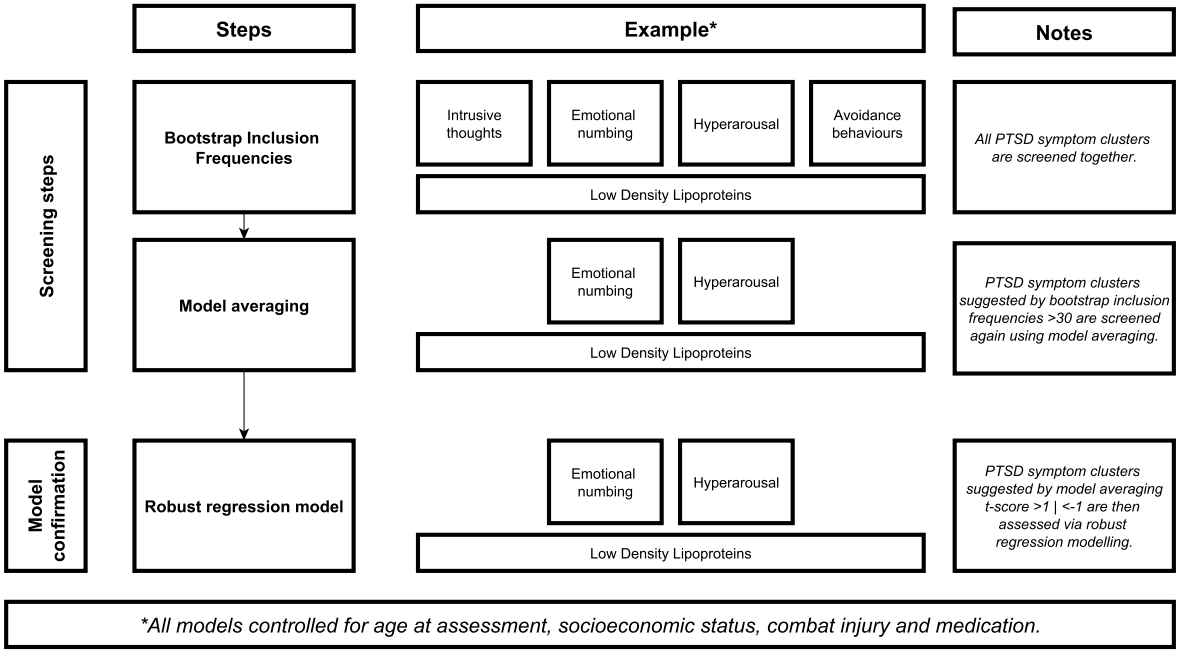

Fig. 1. Variable selection procedures.

Robust regression modelling

Associations suggested by the variable selection procedures were confirmed via the use of robust regression using MM maximum likelihood type estimation (Yohai, 1987). This approach allows the inclusion of observations with residual outliers by assigning weights to the outlier residuals to reduce their impact on the overall model. Models were generated at a univariable and multivariable level including confounders. Models were bootstrapped using at least 1000 replications and bias-corrected confidence intervals are reported. Non-linear relationships were assessed with restricted cubic spline functions of the PTSD symptom cluster and are only presented in figure form. Estimated levels of associated cardiovascular outcomes were generated from margins of the outcome over PTSD symptom cluster scores.

Missing data

Missing values ranged from 3 observations (did not complete PCL; <1%) to 55 observations (LDL; 4.8%). 14 participants had one item missing and one participant had two items missing from the PCL. These missing items were imputed using two way imputation (Van Ginkel et al., 2007). All other dependent variable missing data was handled using casewise deletion. 1145 participants were seen as part of the baseline ADVANCE study visit. Exclusion criteria from current analysis included: missing PCL scores (3 observations; <1%); likely current acute infection (HsCRP levels >10: 30 observations; 2.7%); experienced significant injury outside of military service (1 observation; <1%). A total of 34 participants were excluded.

3. Results

$n = 1111/1145$ participants were included as part of this analysis. Table 1 describes the demographic characteristics of the ADVANCE cohort stratified by probable PTSD status. Median age of the cohort at assessment was 33 years (IQR 30, 37), $n = 137$ were of officer rank (12.33%) and $n = 554$ sustained a combat injury (50.14%). 110 participants (9.89%) were on a medication of interest; sertraline was the most common mental health medication ($n = 24$) and allopurinol was the most common cardiovascular medication ($n = 5$). 138 participants indicated probable PTSD based on their PCL scores (12.14%) and $n = 974$ did not (87.86%). Supplementary materials 2 shows Spearman's correlation coefficients between PTSD symptom clusters, confounders and cardiovascular risk outcomes. Moderate to strong correlations were noted between the PTSD symptom clusters.

Results from the variable selection procedures can be found in supplementary materials 3. No associations were noted between PTSD symptom clusters with (log)HsCRP, DBP, total cholesterol, or $HbA1_C$. The avoidance behaviours symptom cluster was selected for PWV. The hyperarousal symptom cluster was selected for outcomes of HDL, LDL and (log)triglyceride levels. The emotional numbing symptom cluster was selected for the outcomes of insulin resistance, LDL and resting heart rate. The intrusive thoughts symptom cluster were selected for, HDL, insulin resistance and visceral adipose tissue. The avoidance behaviours and intrusive thoughts symptom clusters were selected together for SBP. The emotional numbing and hyperarousal symptom clusters were selected together for LDL. Non-linear relationships were noted between the emotional numbing symptom cluster and resting heartrate as well as the intrusive thoughts symptom cluster and SBP. Whilst the emotional numbing and intrusive thoughts symptom clusters were selected independently for insulin resistance, the intrusive thoughts model was unable to converge due to an issue with the inclusion of age at assessment as a covariate. The robust regression model for insulin resistance and intrusive thoughts excluding age as a covariate is shown in supplementary materials 4.

Table 2 reports the associated robust regression coefficients between each symptom cluster and cardiovascular risk factor selected by the

Table 1
Demographic characteristics of ADVANCE cohort, stratified by probable post-traumatic stress disorder status.

	Overall sample (n = 1111)	No PTSD (n = 973)	Probable PTSD (n = 138)
Demographics			
Ethnicity			
White *n* (%)	1007 (90.64)	875 (89.93)	132 (95.65)
All other ethnic groups *n* (%)	104 (9.36)	98 (10.07)	6 (4.35)
Confounders			
Median Age at assessment (IQR)	33 (30, 37)	33 (30, 37)	33 (29, 37)
On cardiovascular or mental health medication			
No *n* (%)	1002 (90.19)	910 (93.53)	92 (66.67)
Yes *n* (%)	109 (9.81)	63 (6.47)	46 (33.33)
Cardiovascular medication *n* (%)	28 (2.52)	22 (2.26)	6 (4.35)
Mental health medication *n* (%)	81 (7.29)	41 (4.21)	40 (28.99)
Combat injury			
No injury *n* (%)	557 (50.14)	506 (52.00)	51 (36.96)
Injury *n* (%)	554 (49.86)	467 (48.00)	87 (63.04)
Socioeconomic status at sampling			
Junior non-commissioned Officer rank *n* (%)	729 (65.62)	617 (63.41)	112 (81.16)
Senior non-commissioned Officer rank *n* (%)	245 (22.05)	220 (22.61)	25 (18.12)
Commissioned Officer rank *n* (%)	137 (12.33)	136 (13.98)	1 (0.72)
Exposure			
PTSD			
PCL Total score Median (IQR)	25.00 (19.00, 36.00)	24.00 (19.00, 30.00)	58.00 (53.00, 69.00)
PCL Hyperarousal score Median (IQR)	9.00 (6.00, 13.00)	8.00 (6.00, 11.00)	20.00 (18.00, 22.00)
PCL Emotional numbing score Median (IQR)	7.00 (5.00, 11.00)	6.00 (5.00, 9.00)	18.00 (16.00, 21.00)
PCL Avoidance behaviours score Median (IQR)	2.00 (2.00, 4.00)	2.00 (2.00, 3.00)	7.00 (6.00, 8.00)
PCL Intrusive thoughts score Median (IQR)	6.00 (5.00, 9.00)	6.00 (5.00, 8.00)	17.00 (14.00, 20.00)
Outcomes *Associated clinical normal ranges*			
Inflammation			
HsCRP (mmol/l) Median (IQR) *Normal range <1.0 mmol/l*	0.90 (0.50, 1.80)	0.90 (0.49, 1.80)	0.95 (0.55, 1.95)
HsCRP (mmol) Geometric mean 95%CI	0.94 (0.89, 1.00)	0.93 (0.88, 0.99)	1.05 (0.89, 1.22)
Haemodynamic functioning			
Resting heart rate (BPM) Median (IQR) *Normal resting heart rate 50-80BPM*	57.00 (51.67, 63.00)	56.67 (51.00, 62.00)	59.33 (55.00, 66.67)
Diastolic blood pressure (mmHg) Median (IQR) *Normal diastolic blood pressure: <80 mmHg*	73.00 (67.67, 79.33)	73.00 (67.67, 79.33)	73.00 (68.00, 78.67)
Systolic blood pressure (mmHg) Median (IQR) *Normal systolic blood pressure: <120 mmHg*	129.00 (122.67, 136.67)	129.00 (123.00, 136.67)	129.50 (121.33, 137.00)
Pulse wave velocity(m/s) Median (IQR) *Normal pulse wave velocity range: 4.2-9.4 m/s*	7.77 (7.07, 8.70)	7.77 (7.03, 8.70)	7.77 (7.07, 8.80)
Cardiometabolic effects			
Triglycerides (mg/dl) Median (IQR) *Normal triglycerides: <150 mg/dl*	97.43 (70.86, 141.71)	97.43 (70.86, 132.86)	124.00 (79.71, 168.28)
Triglycerides (mg/dl) Geometric mean (95%CI)	104.31 (101.03, 107.70)	102.01 (98.61, 105.53)	122.08 (111.41, 133.77)
Total Cholesterol (mg/dl) Median (IQR) *Normal cholesterol: <200 mg/dl*	189.48 (166.28, 216.55)	189.48 (166.28, 212.69)	185.62 (166.28, 216.55)
High Density Lipoproteins (mg/dl) Median (IQR) *Normal High Density Lipoproteins: 40-60 mg/dl*	50.27 (42.54, 58.01)	50.27 (42.54, 58.01)	46.40 (38.67, 50.27)
Low Density Lipoproteins (mg/dl) Median (IQR) *Normal Low*			

(*continued on next page*)

Table 1 (*continued*)

	Overall sample (n = 1111)	No PTSD (n = 973)	Probable PTSD (n = 138)
Density Lipoproteins: <130 mg/dl	116.01 (96.68, 139.21)	116.01 (96.68, 139.21)	112.14 (96.68, 139.21)
$HbA1_C$ (mmol/mol) Median (IQR) *Normal:* <42 mmol/mol	34.00 (32.00, 36.00)	34.00 (32.00, 36.00)	35.00 (32.00, 36.00)
Insulin resistance (mg/kg/min) Median (IQR) *Indicative of metabolic syndrome* ≤*8.77* mg/kg/min	9.81 (9.02, 10.38)	9.86 (9.10, 10.39)	9.47 (8.65, 10.25)
Visceral Adipose Tissue (cm^2) Median (IQR) *Normal:* <100 cm^2	86.25 (64.64, 113.83)	85.35 (67.11, 111.95)	93.56 (72.80, 131.43)

Acronyms: BPM Beats per minute; CI Confidence Interval; IQR Interquartile range; PCL Posttraumatic stress disorder clinical checklist PTSD Post traumatic stress disorder.

Table 2
Robust regression coefficients of post-traumatic stress disorder symptom clusters with linear relationships to cardiovascular risk outcomes.

Cardiovascular risk outcome	Post-Traumatic Stress Disorder symptom cluster	Model 1[a] coefficient (95% bias-corrected confidence interval)	Model 2[b] coefficient (95% bias-corrected confidence interval)
Pulse Wave Velocity	Avoidance behaviours (score range from 2 to 10)	0.038 (0.000, 0.080)	0.033 (−0.008, 0.076)
Systolic blood pressure	Avoidance behaviours (score range from 2 to 10)	0.785 (0.189, 1.309)	0.640 (0.065, 1.149)
Insulin resistance	Emotional numbing (score range from 5 to 25)	−0.031 (−0.047, −0.162)	−0.021 (−0.036, −0.005)
Low Density Lipoproteins	Emotional numbing (score range from 5 to 25)	0.389 (−0.368, 1.098)	0.476 (−0.237, 1.358)
	Hyperarousal (score range from 5 to 25)	−0.612 (−1.272, 0.068)	−0.553 (−1.222, 0.122)
High Density Lipoproteins	Hyperarousal (score range from 5 to 25)	−0.247 (−0.371, −0.119)	−0.122 (−0.267, 0.016)
(Log) Triglycerides[c]	Hyperarousal (score range from 5 to 25)	1.015 (1.008, 1.021)	1.009 (1.002, 1.017)
High Density Lipoproteins	Intrusive thoughts (score range from 5 to 25)	−0.299 (−0.454, −0.154)	−0.159 (−0.312, 0.002)
Visceral Adipose Tissue	Intrusive thoughts (score range from 5 to 25)	0.862 (0.312, 1.539)	0.574 (0.020, 1.250)

[a] Univariable model including PTSD symptom cluster.
[b] Multivariable model including PTSD symptom cluster and confounders (age at assessment, combat injury, medication use and socioeconomic status).
[c] Coefficients are exponentiated and refer to percentage change in geometric mean of triglyceride levels. E.g. 1.015 = 1.5% increase.

variable selection procedures. At a univariable level, robust regression confirmed all associations between all symptom clusters and cardiovascular outcomes apart from LDL with emotional numbing or hyperarousal. After adjusting for confounders the following associations failed to be confirmed: hyperarousal and intrusive thoughts with HDL, emotional numbing and hyperarousal with LDL and avoidance behaviours with PWV. Confirmed robust regression models suggested that increasing severity of symptoms in the avoidance behaviours symptom cluster was associated with greater SBP. Severity of symptoms in the emotional numbing symptom cluster was associated with greater insulin resistance and had a non-linear association with heart rate. Severity of symptoms in the hyperarousal symptom cluster was associated with greater levels of triglycerides. Severity of symptoms in the intrusive thoughts symptom cluster were associated with greater visceral adipose tissue and had a non-linear association with SBP. Figs. 2–6 visualises the linear and non-linear relationships between the symptom clusters and their associated cardiovascular risk outcomes. Supplementary materials 5 shows the figures for variables not confirmed by robust regression modelling.

4. Discussion

In this study we aimed to assess the association between PTSD symptom clusters and cardiovascular risk, hypothesising that the hyperarousal symptom cluster would be most likely to be associated with greater relative cardiovascular risk. Contrary to our hypothesis, we found that a diverse number of PTSD symptom clusters were suggested as the most relevant symptom clusters associated with both cardiometabolic effects and haemodynamic functioning and no PTSD symptom clusters were associated with inflammation, specifically inflammatory marker HsCRP. Increased severity of symptoms in the avoidance behaviours symptom cluster was associated with haemodynamic functioning, specifically SBP and PWV. Severity of symptoms in the emotional numbing symptom cluster was associated with cardiometabolic effects and haemodynamic functioning, specifically resting heart rate, HDL and insulin resistance. Severity of symptoms in the hyperarousal symptom cluster were associated with cardiometabolic effects, specifically triglyceride levels, HDL and LDL levels. Severity of symptoms in the intrusive thoughts cluster was associated with cardiometabolic effects and haemodynamic functioning, specifically visceral adipose tissue, HDL and SBP. However not all these relationships were linear, with emotional numbing and intrusive thoughts symptom clusters showing evidence of non-linear associations with resting heart rate and SBP. Evidence for associations between PTSD symptom clusters with PWV, HDL and LDL was limited, as whilst each of the clusters were selected by variable selection procedures, they were not confirmed by robust regression modelling. The magnitude of the associations between any symptom cluster and cardiovascular risk outcome were small/modest.

This study used the symptom clusters reflective of the Diagnostic Statistical Manual-IV (DSM-IV). The latest version of the DSM (DSM-V) acknowledges a standard hyperarousal model of PTSD as well as a dissociative model of PTSD. In the hyperarousal model, patients are more likely to report recurrent, intense flashbacks and/or recollections of the traumatic event that cause distress. In the dissociative model, patients also experience depersonalisation or derealisation, symptoms primarily associated with feeling detached from themselves or from the world around them. It is theorised that each of these subtypes may present with mechanistically different physiological responses to stress. Comparisons of the two subtypes have found that the hyperarousal subtype is more likely to show increases in heart rate when exposed to traumatic-script driven imagery, whereas the dissociative subtype showed no change or a decrease in heart rate (Lanius et al., 2002; RuthLanius et al., 2010; Wolf et al., 2012). Unique neurobiological features of the dissociative subtype of PTSD are theorised to be responsible for the blunted autonomic response (Boulet et al., 2022). Heart rate is a simple proxy for autonomic response and in our study we found a non-linear relationship between heart rate and emotional numbing. It is possible that some of our cohort might exhibit dissociative symptoms alongside their PTSD, however questionnaires used within the ADVANCE cohort currently do not assess dissociation, so it is unclear how much of an effect depersonalisation or derealisation symptoms

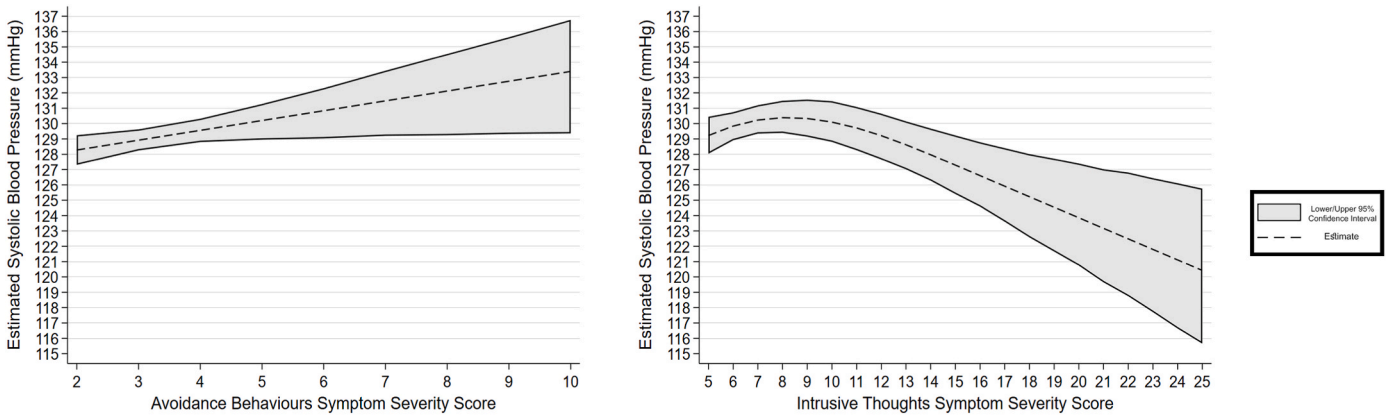

Fig. 2. Estimated marginal effects of post-traumatic stress disorder symptom clusters selected for the systolic blood pressure model by variable selection procedures and confirmed by robust regression modelling.

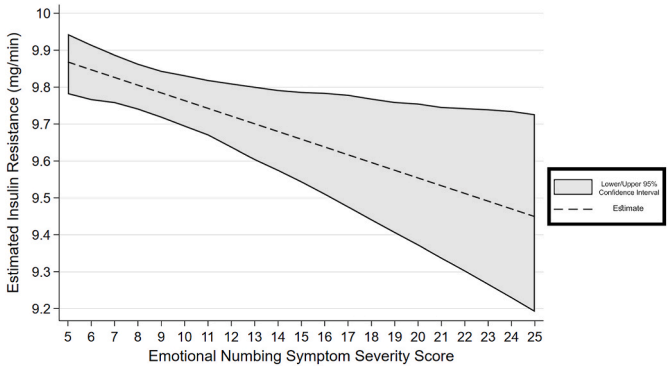

Fig. 3. Estimated marginal effects of post-traumatic stress disorder symptom clusters selected for the insulin resistance model by variable selection procedures and confirmed by robust regression modelling.

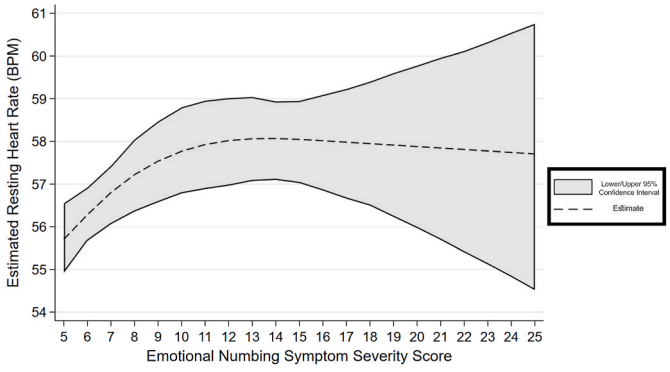

Fig. 4. Estimated marginal effects of post-traumatic stress disorder symptom clusters selected for the resting heart rate model by variable selection procedures and confirmed by robust regression modelling.

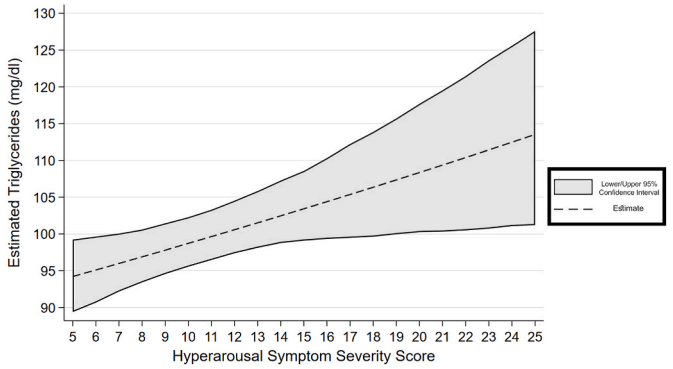

Fig. 5. Estimated marginal effects of post-traumatic stress disorder symptom clusters selected for the (log)triglycerides model by variable selection procedures and confirmed by robust regression modelling.

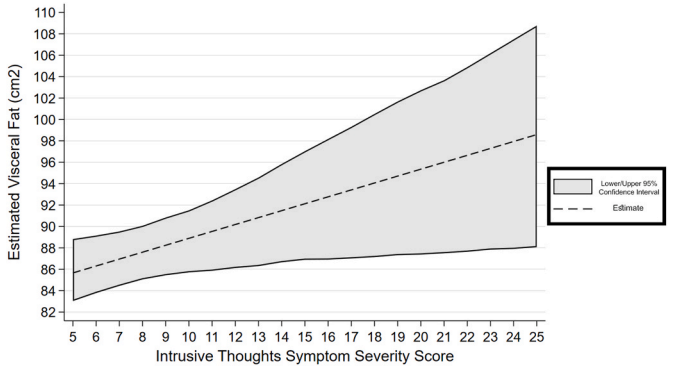

Fig. 6. Estimated marginal effects of post-traumatic stress disorder symptom clusters selected for the visceral adipose tissue model by variable selection procedures and confirmed by robust regression modelling.

have on our observed associations between PTSD and cardiovascular response.

One alternative theory suggests that hyperarousal symptoms are a product of processing from the amygdala, from which modulations of other areas of the brain such as the brain stem, can result in hyperarousal symptoms including an exaggerated startle response (Weston, 2014). Emotional numbing is theorised to be a product of over stimulation of these hyperarousal symptoms, which result in emotional exhaustion/depletion of cognitive resources (Weems et al., 2003). Some evidence exists regarding an association between cortisol, a primary hormone associated with HPA regulation, and emotional numbing, with greater emotional numbing severity resulting in flatter cortisol awakening responses (Garcia et al., 2020). Similarly, greater severity of emotional numbing symptoms have been associated with lower cortisol excretion 6 months after experiencing a motor vehicle accident in those exhibiting PTSD symptomology (Hawk et al., 2000). It is possible that those with the most severe emotional numbing symptoms represent a group with depleted cognitive resources that have a reduced effect on cardiovascular/nervous system responses.

Intrusive thoughts were found to be associated with greater visceral

adipose tissue and had a nonlinear association with SBP. It is likely there is a significant overlap between the symptom clusters of intrusive thoughts and hyperarousal. One question on the intrusive symptom cluster refers to having 'physical reactions (e.g. heart pounding, trouble breathing or sweating) when something reminded you of a stressful experience'. Increased severity of intrusive thoughts might reflect more opportunities for a hyperarousal response, and it is likely through these mechanisms that it was found to have associations with cardiovascular risk outcomes. However, PTSD symptom clusters could also affect other factors associated with haemodynamic functioning and cardiometabolic effects, such as sleep, diet, physical inactivity, alcohol use or depression (Aaseth et al., 2019; van den Berk-Clark et al., 2018b). It is possible for example, that participants with intrusive thoughts might use physical exercise as a coping mechanism, which might explain why, as intrusive thoughts become more severe, SBP decreased (Adams et al., 2020). Such mediating factors could also explain the limited/mixed evidence we observed for an association between PTSD symptom clusters and cholesterol (HDL and LDL) or PWV. Longitudinal assessment of mediating factors between PTSD symptom clusters and cardiovascular risk might help shed light on the specific roles these symptoms have on cardiovascular systems.

The ADVANCE cohort is a sample representative of UK combat injured personnel, approximately half of which sustained a combat injury and the other half frequency matched to the injured group but without sustaining an injury (Boos et al., 2021). It is still likely that a significant part of this cohort, whilst including those with serious combat injuries, also represents a group with increased physical fitness compared to the general population, previously defined as 'the healthy soldier/warrior/worker effect' (Bergman et al., 2019). Even so, we observed worse cardiovascular profiles amongst those who exhibited more severe PTSD symptoms within each symptom cluster. Whilst our findings were generally within the normal clinical ranges for these cardiovascular outcomes, it is likely that our observed increase in relative cardiovascular risk is potentially an early sign of later worsening cardiovascular health, though longitudinal research is required to understand whether these early associations translate into longer term risk or disease. If confirmed by longitudinal analysis, Medical Force Protection, the Armed Forces strategy for maintaining healthy military personnel, as well as UK NHS services, might benefit from assessment and targeting of those with specific symptoms and identify early intervention or monitoring strategies to mitigate the increased CVD risk. Evidence already exists for the benefits of implementing mental health assessment in general hospital settings (Rayner et al., 2014). Assessing for PTSD symptoms in this manner, particularly amongst those already at risk due to previous CVD events such as myocardial infarction or have other CVD risk factors such as diabetes mellitus, might help identify patients who could benefit both psychologically and physiologically from psychological interventions.

This study investigated a comprehensive CVD risk portfolio based on a-priori reasoning and used a robust statistical approach regarding variable selection procedures. However, this study has several limitations. The presence of residual outliers required the use of robust regression models, which is currently incongruent with packages available for variable selection procedures in STATA. All variable selection procedures were based on linear regression models, which led to some symptom clusters being selected but not confirmed by the robust regression methodology. This dataset is currently cross-sectional and purely an assessment of association, not causality. Our use of the PCL-C to measure PTSD and subsequent use of the four factor subscale scores is reflective of the DSM-IV and not the current DSM-V disorder. Future follow ups of the ADVANCE cohort will implement the PCL-5. Another limitation is that no questions regarding dissociative symptoms were asked, and it is likely that those experiencing these types of symptoms have very different cardiovascular responses to stress (Lanius et al., 2002; RuthLanius et al., 2010; Wolf et al., 2012). It is likely that lifestyle factors such as diet, exercise or smoking, as well as comorbid depression at least partially mediate the relationship between PTSD and CVD (van den Berk-Clark et al., 2018b). Mediation analysis was beyond the scope of this current analysis, and assessment of depressive symptoms was not possible due to the large amount of mental health multimorbidity observed in the study (Dyball et al., 2022). Finally, this cohort was comprised of male personnel only. Whilst both women and men who experience PTSD are at greater risk of CVD, the mechanisms by which this occurs are likely to be different, and so our results should only be extrapolated to males with PTSD (Seligowski and Ressler, 2022).

In a cohort of UK male military personnel who deployed to Afghanistan, PTSD symptom clusters were associated with mechanisms for cardiovascular disease including cardiometabolic effects and haemodynamic functioning, but not inflammation (through inflammatory marker HsCRP). Evidence that PTSD is not a homogenous disorder and that a complex pattern of symptoms best describe associations with cardiovascular health is present. Future research should clarify whether these associations are fully or partially mediated by lifestyle factors such as physical activity, diet, alcohol use or smoking.

Author statement

Daniel Dyball: Conceptualisation; methodology; validation; formal analysis; data curation; data curation; formal analysis; writing (original draft); writing (review and editing); visualisation.

Alexander N Bennett: Conceptualisation; funding acquisition; methodology; supervision; writing (review).

Susie Schofield: Methodology; validation; data curation; formal analysis; writing (review).

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Anthony MJ Bull: Conceptualisation; funding acquisition; methodology.

Sharon AM Stevelink: Methodology; supervision; writing (review).

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.01.010.

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