Journal of Affective Disorders 375 (2025) 86–92

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Post-traumatic stress disorder (PTSD) symptom clusters associated with an indicator of heart rate variability: The ADVANCE cohort study

Daniel Dyball [a,1,*], Rabeea Maqsood [b,c,1], Susie Schofield [c], Alexander N. Bennett [d], Paul Cullinan [c], Anthony M.J. Bull [e], Christopher J. Boos [b,2], Nicola T. Fear [a,f,2], on behalf of the ADVANCE Study

[a] King's Centre for Military Health Research, King's College London, SE5 9RJ, United Kingdom of Great Britain and Northern Ireland
[b] Faculty of Health & Social Sciences, Bournemouth University, Bournemouth BH1 3LT, United Kingdom of Great Britain and Northern Ireland
[c] National Heart and Lung Institute, Faculty of Medicine, Imperial College London, SW3 6LR, United Kingdom of Great Britain and Northern Ireland
[d] Academic Department of Military Rehabilitation, Defence Medical Rehabilitation Centre, Stanford Hall Estate, near Loughborough, Nottinghamshire LE12 5BL, United Kingdom of Great Britain and Northern Ireland
[e] Centre for Blast Injury Studies, Department of Bioengineering, Imperial College London, SW7 2AZ, United Kingdom of Great Britain and Northern Ireland
[f] Academic Department of Military Mental Health, King's College London, SE5 9RJ, United Kingdom of Great Britain and Northern Ireland

ARTICLE INFO

Keywords:
Stress Disorders
Post-Traumatic
Heart disease risk factors
Military personnel
Afghanistan
ADVANCE study cohort

ABSTRACT

Background: Heart rate variability (HRV) is governed by sympathetic and parasympathetic regulatory systems. Post-Traumatic Stress Disorder (PTSD) may influence these systems and consequently affect cardiovascular functioning.

Methods: The sample consisted of 860 UK male military personnel approximately half of whom had sustained physical combat injuries in Afghanistan. HRV was measured via Root-Mean Square of Successive Differences (RMSSD) in normal heart beats and PTSD using a self-report questionnaire (Posttraumatic Checklist-Civilian version (PCL)). Associations between probable PTSD status (PCL score $\geq$ 50) and symptom clusters (avoidance behaviours, emotional numbing, hyperarousal and intrusive thoughts) with HRV were examined. Bootstrap inclusion frequencies and model averaging were employed prior to regression modelling to identify the most important symptom clusters associated with RMSSD.

Results: Probable PTSD status was not associated with log RMSSD [−11.6 % (95 % Confidence Interval (CI) -22.2 %, 4.1 %). Increases in severity of emotional numbing were associated with reductions in RMSSD, with a − 1.1 % (95%CI -2.1 %, −0.2 %) decrease in the geometric mean of RMSSD per point increase on the emotional numbing subscale.

Limitations: High levels of comorbidity with depression/anxiety; possible endogeneity/bidirectionality due to PCL including both psychological and physiological symptoms.

Conclusions: Emotional numbing, the symptom cluster including symptoms such as anhedonia, cognitive dysregulation and feeling distant from other people, was associated with lower HRV whilst overall PTSD status was not. These results lend support to the hypothesis that different PTSD symptom clusters may have unique effects on the cardiovascular system, and that particular symptom clusters of PTSD or combinations thereof may be associated with distinctive cardiovascular profiles.

1. Introduction

Heart rate variability (HRV) refers to the variation in time interval between consecutive heart beats (Malik, 1996). The use of HRV as a marker of autonomic function has increased given its objectivity and feasibility in measurement (Billman et al., 2015). Traditionally, HRV

* Corresponding author at: King's Centre for Military Health Research, King's College London, Weston Education Centre, Cutcombe Road, SE5 9RJ, United Kingdom of Great Britain and Northern Ireland.
E-mail address: daniel.dyball@kcl.ac.uk (D. Dyball).
[1] Joint first authors
[2] Joint last authors

https://doi.org/10.1016/j.jad.2025.01.087
Received 20 May 2024; Received in revised form 16 January 2025; Accepted 18 January 2025
Available online 20 January 2025
0165-0327/© 2025 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/).

data can be acquired using an electrocardiogram (ECG) recording over durations varying from 10 to 300 s (ultra-short term/short-term) up to long term (24 h) (Shaffer and Ginsberg, 2017). As a reflection of autonomic imbalance, low HRV is now understood to be a marker of increased risk of cardiovascular disease and may be a useful tool to identify at risk populations (Fang et al., 2020; Orini et al., 2023).

Mental health is one of the key factors that influences HRV. Mounting evidence confirms reduced HRV corresponding to autonomic dysregulation arising from poor mental health. Post-Traumatic Stress Disorder (PTSD) is characterised by symptoms such as intrusive thoughts, emotional dysregulation (often called either emotional numbing or negative alterations in cognitions or mood in the scientific literature), hyperarousal and engaging in avoidance behaviours. These symptoms are thought to impact on health behaviours that increase risk of cardiovascular disease, such as increased smoking of tobacco and alcohol use. Additional mechanisms include direct effects on the autonomic system, with evidence of cardiometabolic (Dyball et al., 2023; Rosenbaum et al., 2015), haemodynamic (Dyball et al., 2019) and inflammatory responses (Passos et al., 2015). A series of meta-analyses have also confirmed lower parasympathetic tone manifested by attenuated HRV in individuals with PTSD diagnosis (Ge et al., 2020; Schneider and Schwerdtfeger, 2020), highlighting HRV as a psychophysiological marker of PTSD (Nagpal et al., 2013).

While PTSD is known to be associated with various manifestations of the cardiovascular system, the specific psychological mechanisms by which this occurs are still largely unknown. Hyperarousal symptoms are hypothesised as being the main contributory mechanism, through dysregulated hypo-pituitary adrenal functioning, greater cardiovascular reactivity and disordered sleep, though few studies have investigated this (Brudey et al., 2015; Presciutti et al., 2020). A recent analysis from the ADVANCE cohort, a longitudinal study investigating the long-term health impact of sustaining a physical combat injury, found that the relative importance of several symptoms, not just hyperarousal, best explained associations between PTSD and a range of cardiometabolic and haemodynamic effects (Dyball et al., 2023).

This analysis presents information on RMSSD, a marker of HRV, among a cohort of UK military personnel (the ADVANCE cohort), stratified by probable PTSD status. We then use variable selection procedures to select symptom clusters of PTSD based on their relative importance in explaining associations with HRV. We hypothesise that probable PTSD will be associated with lower RMSSD compared to those without probable PTSD, and hyperarousal symptoms will be selected as the most relatively important symptom cluster.

2. Methods

2.1. Study design and participants

The ArmeD serVices trAuma rehabilitatioN outComE (ADVANCE) study cohort was set up to investigate the long-term physical and psychosocial health of UK military personnel who sustained a physical combat injury while on deployment in Afghanistan (Bennett et al., 2020), of which the inclusion/exclusion criteria can be found in **Supplementary materials 1**. 579 male UK military personnel who sustained a serious physical combat injury in Afghanistan which required them to be aeromedically evacuated to a UK hospital took part in the study, alongside a demographically similar comparison group of 566 male personnel who sustained no serious physical injuries during their deployment. The latter were frequency-matched to the injured group on age, rank, regiment, role on deployment, service and deployment era. The cohort was recruited from a sample provided by the Ministry of Defence, Defence Statistics (UK). This analysis utilises the baseline dataset of this cohort.

2.2. Procedure

Participants were assessed at the Defence Medical Rehabilitation Centre Headley Court (2015–2018) or Stanford Hall (2018–2020), where they underwent a comprehensive set of physical health tests as well as a clinical interview with a research nurse and a confidential self-report questionnaire. This analysis utilises data from the Vicorder assessment and self-report questionnaire for PTSD.

2.3. Ethics

The ADVANCE study has full approval from the UK 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

2.4.1.1. Post-traumatic stress disorder (PTSD). PTSD was assessed via the PTSD Clinical Checklist-Civilian (PCL-C), a 17-item questionnaire (Blanchard et al., 1996). Possible scores range from 17 to 85, with higher scores reflecting greater symptom severity. Probable PTSD was defined by a score of $\geq$50 (Weathers et al., 1993). The four-factor solution of this measure was employed based on DSM-IV criteria for PTSD (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). Cronbach's alpha from this cohort overall was 0.95, with subscale scores ranging from 0.81 (avoidance behaviours) to 0.92 (intrusive thoughts).

2.4.2. Outcome

2.4.2.1. Heart rate variability. This analysis reports Root Mean Squared of Successive Differences (RMSSD) as a measure of ultra-short term HRV (HRV_{UST}). RMSSD was included given its traditional use as a marker of parasympathetic tone (Malik, 1996) and established reliability and validity in HRV_{UST} analysis (Munoz et al., 2015; Nussinovitch et al., 2011; Thong et al., 2003). The HRV_{UST} data was quantified using the cardiac inter-beat intervals from femoral arterial waveforms (up to 16 s in length) recorded during the pulse wave velocity measurement using the Vicorder device (Skidmore Medical, Bristol, UK). The Vicorder assessment has been described and validated previously (Bennett et al., 2020; Pucci et al., 2013).The use of $RMSSD_{UST}$ (14 s) for HRV measurement has been found to be as reliable and valid as the 300 s ECG-based short-term RMSSD in the ADVANCE study cohort (Maqsood et al., 2023a, 2023b; Maqsood et al., 2024).

Participants were asked to fast for at least 8 h and refrain from smoking for at least 4 h prior to assessment. Participants were encouraged to avoid talking or moving during the assessment. All measurements took place on a hospital bed in supine position in a temperature and noise-controlled room during the daytime. Participants breathed spontaneously throughout the Vicorder assessment.

Kubios premium (Kubios Premium V.3.2, The Biomedical Signals Analysis and Medical Imaging Group, University of Kuopio, Finland) was used for HRV analysis following the import of the femoral arterial waveforms from the Vicorder device. The noise was set to medium and automatic correction to none; this was further supplemented by visual inspection and correction of signals, wherever needed due to ectopic or erroneous beats. We set the signal analysis type to 'single' for >10 s recording and to 'merge' for <10 s recording. The method of analysis has been described in detail elsewhere (Maqsood et al., 2023a, 2023b).

2.4.3. Confounding variables

2.4.3.1. Age at assessment. Age in years at time of ADVANCE baseline assessment was used.

2.4.3.2. Combat injury. Combat injury was established from Defence Statistics (Health) records and supplemented by the research-nurse led clinical interview. Combat injury was coded as uninjured, non-amputation injured and amputation injured. Amputation injuries were defined by major limb amputation (e.g. transhumeral, transtibial); isolated partial amputation (e.g. digit, toe, partial foot) alone were not included in this group unless accompanied by major limb amputation.

2.4.3.3. Medication. Medications currently being used by participants identified during the clinical interview were coded with the Anatomical Chemical Classification Index 2020 (World Health Organisation Collaboration Centre for Drug Statistics Methodology, 2020). Medications of interest included medications that affected the cardiovascular system 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 based on being on a medication of interest or not being on any of the above medications.

2.4.3.4. Socioeconomic status. Rank at time of sampling (e.g. deployment of interest/injury) was used to indicate socioeconomic status; Other rank/junior non-commissioned officer (NATO OR2-OR4), Senior non-commissioned officer (NATO OR5-OR9) and Commissioned officer (NATO OF1-OF6) (Yoong et al., 1999).

2.5. Data analysis

Data analysis was conducted using the statistical software package STATA version 18.0. Henceforth, the term confounders will refer specifically to age at assessment, combat injury, current medication use and socioeconomic status (Alvares et al., 2016; Maqsood et al., 2023b; Steptoe et al., 2002; Voss et al., 2015). Spearman's correlations were calculated between all variables. Strong correlations were defined as Spearman's correlation coefficients $\geq$0.70 and moderate were defined as $\geq$0.4 & $<$ 0.7. Symptom clusters were assessed in all analyses regardless of probable PTSD status. Sampling weights and response weights were calculated and applied to demographic tables. Weighted percentages alongside 95 % Confidence Intervals (CI) are presented alongside unweighted cell counts.

Regression diagnostics using total PCL score were completed including visual assessment of normality of residuals, residual versus fitted plot, leverage, Variance Inflation Factor (VIF) and Cook's D. Residual outliers were defined as Cook's D $>$ 4/n, where n is the total sample size. 5.8 % ($n = 50$) of the sample were defined as outliers in the global model (including all PTSD symptom clusters), and 5.3 % ($n = 47$) in the final model. RMSSD achieved residual normality after log-transformation. Coefficients for the log-transformed models were exponentiated and are presented as percentage change in geometric mean values. VIF in global models with all symptom clusters included was high but acceptable (VIF: 2.65–3.52; 1/VIF 0.28–0.38). Non-linear associations were assessed via visual inspection of the augmented component plus residual plot. Variables with plots suggestive of non-linear associations were transformed via restricted cubic splines. Likelihood ratio tests were then conducted to confirm whether linear (subscale total score) or non-linear (restricted cubic spline of subscale total score) best fit the model ($p < .05$).

2.5.1. Symptom cluster selection procedure

Variable selection procedures were conducted in line with current best practice (Heinze et al., 2018; Sauerbrei et al., 2020). First, Bootstrap Inclusive Frequencies were generated with all PTSD symptom clusters and confounders using linear regression models utilising 1000 bootstrap replications. Independent variables were assessed with 1 degree of freedom, then repeated with no limits of degrees of freedom to assess non-linear relationships. Co-dependence, i.e. when two or more variables inclusion frequencies are dependent on one another, was investigated between PTSD symptom clusters via interrogation of the chi2 2 $\times$ 2 inclusion frequency tables. If co-dependence was observed, i.e. the bootstrap inclusion frequencies in the chi2 tables were found to be significantly dependent on one another ($p < .05$), strategies for choosing which symptom cluster should be included in the presence of weak associations were applied as detailed in De Bin and Sauerbrei (2018). Second, PTSD symptom clusters that were selected for inclusion (defined as $>$30 % bootstrapped inclusion frequency) were then subject to Weighted Absolute Least Squares model averaging, again with 1000 bootstrap replications. Variables with a t-score $>$ 1 or $<$ −1 and standard error bands that did not cross 0 were selected for the final model. These steps were repeated excluding residual outliers. If a symptom cluster was selected in either the overall or outlier-excluded models the symptom cluster was considered for inclusion in the final model.

2.5.2. Regression modelling

Finally, linear regression models are presented with bias-corrected 95 % Confidence Intervals (CI) from 1000 bootstrap replications. Two models adjusted for confounders are presented; the first uses probable PTSD status (based on PCL score $\geq$ 50) and the second uses the symptom cluster/clusters selected by the symptom cluster selection procedure.

2.5.3. Missing data

Fourteen participants had one item missing from the PCL and one participant had two items missing. Two-way imputation was used to impute these missing items (Van Ginkel et al., 2007). A total of 285/1145 participants (24.9 %) were excluded due to; participants having incomplete/missing arterial waveform data ($n = 282$); participants did not complete the PCL ($n = 3$); participants with likely acute infection at time of assessment (HsCRP levels $>$10; $n = 30$); participants who experienced injury outside of military service ($n = 1$). No differences in the distributions of rank, combat injury, rates of PTSD or ethnicity were observed between those with complete arterial waveform and incomplete/missing arterial waveform (data available upon request).

3. Results

A total of 860/1145 participants (75.1 %) were included in this analysis (Table 1). Participants had a median age of 33 years and attended the ADVANCE study a median of eight years following injury/deployment of interest. Participants were predominantly other rank/junior Non-Commissioned Officers, of white ethnic background, and were not on a medication of interest. 93/860 participants (12.1 %) had probable PTSD. Personnel with probable PTSD exhibited lower RMSSD [36 ms (InterQuartile Range (IQR) 24, 59 ms)] compared to those without PTSD (43 (31, 64)). A Spearman's correlation matrix between all included variables can be found in **Supplementary materials 2**. Moderate-strong correlations were observed between each of the symptom clusters only.

A linear regression model investigating probable PTSD status found that PTSD was not associated with log RMSSD in univariable (percentage change in geometric mean − 14.1 % (95%CI -25.0 %, 0.2 %)) or multivariable models (−11.6 % (95%CI -22.2 %, 4.1 %)).

Variable selection procedures suggested that intrusive thoughts, avoidance behaviours and emotional numbing were associated with log RMSSD. Emotional numbing was initially entered into the variable selection procedure as a non-linear variable, transformed via restricted

Table 1
Sociodemographic, PTSD and HRV characteristics of the sample.

	Overall sample $N = 860$	No PTSD $N = 767$	Probable PTSD $N = 93$
Sociodemographic			
Ethnicity % (n)			
White	90.6 % (783)	90.0 % (695)	94.7 % (88)
All other ethnic groups combined	9.4 % (77)	10.0 % (72)	5.3 % (5)
Combat injury			
Sustained no serious combat injury	47.5 % (434)	49.6 % (401)	32.9 % (33)
Sustained a serious combat injury	52.5 % (426)	50.4 % (366)	67.1 % (60)
Age at assessment median (IQR)	33 (30, 37)	33 (30, 37)	33 (29, 37)
Years since sampled deployment/ injury of interest	8 (6, 9)	7 (6, 9)	8 (7, 9)
Socioeconomic status % (n)			
Other rank/junior NCO	71.1 % (558)	69.5 % (484)	82.9 % (74)
Senior NCO/Officer~	28.9 % (302)	30.5 % (283)	17.1 % (19)
Medication % (n)			
On medication of interest	9.5 % (82)	5.9 % (47)	36.2 % (35)
Cardiovascular medication	2.2 % (22)	NR~	NR~
Mental health medication	7.6 % (63)	4.0 % (30)	34.5 % (33)
PTSD median score (IQR)			
PCL-total score	25 (19, 34)	23 (19, 30)	59 (53, 68)
PCL-Avoidance behaviour score[1]	2 (2, 4)	2 (2,3)	7 (6,8)
PCL-Emotional numbing score[2]	7 (5, 10)	6 (5, 9)	18 (15, 21)
PCL-Intrusive thoughts score[3]	6 (5, 9)	6 (5, 8)	17 (14, 20)
PCL-Hyperarousal score[4]	8 (6, 12)	8 (6, 11)	20 (18, 22)
Outcome			
HRV-RMSSD median (IQR), ms	43 (30, 63)	43 (31, 64)	36 (24, 59)
Geometric mean (95%CI)	42.2 (40.6, 43.9)	42.9 (41.2, 44.7)	36.9 (32.2, 42.3)

CI Confidence Interval; HRV Heart Rate Variability; IQR InterQuartile Range NCO; Non-Commissioned Officer; NR Not Reported; PCL PTSD Clinical Checklist; PTSD; Post-Traumatic Stress Disorder; RMSSD Root Mean Square of Successive Differences. Weighted percentages are presented alongside unweighted cell counts.

~ Some categories combined or data suppressed to allow for confidentiality in line with Defence Statistics rounding policy (https://www.gov.uk/government/publications/defence-statistics-policies/ministry-of-defence-disclosure-control-and-rounding-policy).

1. Avoiding thinking/talking about experience; avoiding reminders of experience.
2. Trouble remembering experience; Loss of interest in activities they used to enjoy; feeling distant/cut off from others; feeling emotionally numb; feeling as if future will be cut short.
3. Repeated disturbing memories, thoughts or images from stressful experience; repeated, disturbing dreams about experience; reliving experience; feeling upset at reminders of experience; having physical reactions to reminders of the experience.
4. Trouble falling or staying asleep; feeling irritable or angry; difficulty concentrating; being 'super alert'; feeling jumpy or easily startled.

cubic spline (**Supplementary materials 3**). However, co-dependency was observed between intrusive thoughts and emotional numbing. Following procedures for mitigating co-dependency and subsequent model averaging, only the linear form of emotional numbing was retained for regression modelling.

In the univariable model, there was an associated −1.5 % (95%CI -2.4 %, −0.6 %) decrease in the geometric mean of RMSSD per point increase in the emotional numbing subscale score. In the multivariable model including confounders, there was an associated −1.1 % (95%CI -2.1 %, −0.2 %) decrease in the geometric mean of RMSSD per point increase in the emotional numbing subscale score (Fig. 1).

4. Discussion

In this analysis, we aimed to present data on RMSSD stratified by probable PTSD status in a cohort of UK Armed Forces personnel and assess whether PTSD status or PTSD symptoms were associated with an indicator of HRV. According to our results, we reject the hypothesis that probable PTSD status would be associated with lower RMSSD and that hyperarousal would be selected as the most relatively important symptom cluster in explaining associations with HRV. Whilst we observed that servicemen with probable PTSD had lower HRV (RMSSD), this was not a statistically significant difference. With the utilisation of variable selection procedures, we ascertained that emotional numbing was associated with RMSSD; as severity of emotional numbing symptoms increased, RMSSD decreased.

Previously in the ADVANCE cohort, the relative importance of PTSD symptom clusters were investigated in relation to associations between PTSD and haemodynamic functioning, cardiometabolic effects and inflammation (Dyball et al., 2023). Emotional numbing best explained associations with resting heart rate (beats per minute) and was observed to have a non-linear association with the outcome. In our current analysis, whilst limited evidence of a non-linear association with log RMSSD was present, a linear association between emotional numbing was ultimately selected after accounting for co-dependency of other symptoms. Intrusive thoughts and avoidance behaviours were noted as competing for inclusion in variable selection procedures. This may be reflective of intrusive thoughts being on the causal pathway to emotional numbing symptoms, whereby emotional numbing and avoidance behaviours are a response to states of re-experiencing (e.g. memories, thoughts or psychological re-experiencing of the traumatic event) (Litz et al., 2002). This analysis did not observe significantly lower RMSSD in individuals with PTSD as per previous research (Ge et al., 2020; Park et al., 2017). Considering the fact we observed that emotional numbing was associated with RMSSD, it is possible that PTSD status, a combination of avoidance behaviours, intrusive thoughts, hyperarousal and emotional numbing symptoms according to DSM-IV criteria, introduces noise from symptoms that are not associated with HRV. The influence of emotional numbing symptoms may also be influenced by disassociation, which has been inversely linked to HRV in individuals with PTSD (Hauschildt et al., 2011). It is plausible that individuals with PTSD adopt dissociation as a defence mechanism to cope with trauma manifesting in derealisation and emotional numbing (Beutler et al., 2022). Amygdala hypoactivity has previously been associated with emotional numbing/dissociation symptoms (Forster et al., 2017), which is another mechanism by which PTSD symptoms may affect cardiovascular health (Tawakol et al., 2017). Unfortunately, no indicator of dissociation was available for the ADVANCE study.

Lifestyle factors may mediate the effect between certain PTSD symptoms and the cardiovascular system. Studies investigating US veterans with PTSD have observed that emotional numbing is associated with lower likelihood of exercising daily, whilst intrusive thoughts have been shown to be associated with a greater likelihood of exercising daily (Adams et al., 2020). Direct effects of strenuous exercise on reductions in hyperarousal symptoms and avoidance/numbing have also been observed, although that study used a three factor solution of the PCL (Whitworth et al., 2017). Avoidance/numbing has been suggested as the most relatively important symptom cluster to explain the associations between PTSD and alcohol misuse (Debell et al., 2014). Similarly, avoidance and hyperarousal symptoms are suggested as the most relatively important symptoms in explaining cigarette smoking (Kearns et al., 2018).

The effects of multiple PTSD symptoms on other aspects of HRV and the cardiovascular system have been explored in the scientific literature. Lee et al. found that PTSD symptom clusters have differential relationships with blood pressure and HRV during both reactivity and recovery from a stress task in trauma exposure adults (Lee et al., 2022). Specifically, hyperarousal symptoms were associated with higher HRV (low frequency, high frequency, low/high frequency) during recovery, but avoidance and intrusive thoughts were associated with increases in blood pressure during the task. Additionally, avoidance was association with lower HRV (low frequency and high frequency) whilst emotional

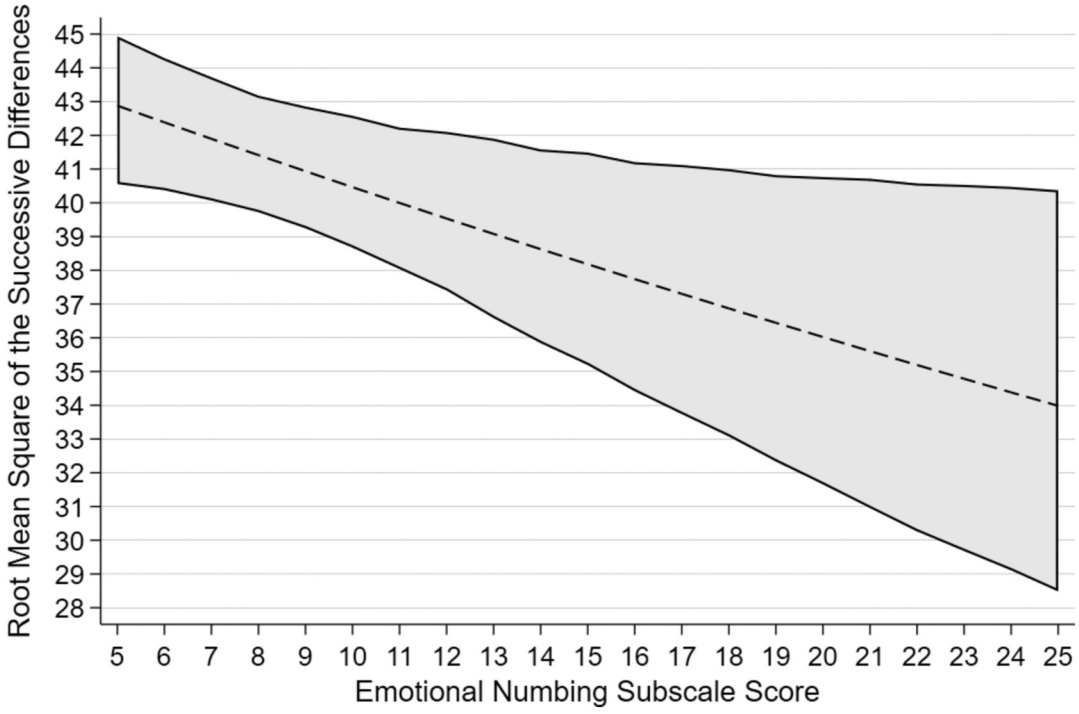

Fig. 1. Estimated marginal effects of the symptom cluster 'Emotional Numbing' association with Heart Rate Variability.

numbing was associated with decreases in blood pressure and low frequency HRV. This, alongside our results, suggest that PTSD symptom clusters may have unique effects on the cardiovascular system, and that different symptom profiles may be associated with distinctive cardiovascular health profiles.

Our findings, along with those of new studies examining the differential symptom effects of PTSD on the cardiovascular system, suggest that clinicians and researchers should not treat those with PTSD as a homogonous group. Rather, clinicians and researchers would benefit from understanding the specific symptom structure that their patients/participants are experiencing and the combinations by which these symptoms might affect cardiovascular responses or risk of cardiovascular disease. Treatments that utilise physical and mental health feedback in synchronicity, such as HRV-biofeedback therapy (synchronised heart rate with breathing techniques), may be considered to elevate HRV and lower PTSD symptoms (Tan et al., 2011). This might also be most effective for emotional numbing which has been reported to show significant improvement with the largest effect size as compared to other PTSD symptoms in response to HRV biofeedback therapy (Schuman and Killian, 2019).

The study is subject to some limitations. While it benefits from a relatively large sample size, a small proportion of HRV data was missing due to technical constraints. This may have affected the sampled representation of PTSD. Participants were asked to bring in all medications they were currently on, however in the case where participants did not bring in their medications, we relied on participants self-reporting details of medication use. It is possible they mis-reported or misremembered medications. Whilst future follow ups of the cohort will utilise the PCL-5, which is based on the DSM-V, this current dataset utilised the PCL—C, which is based on the DSM-IV. Co-dependency between symptom clusters was observed and addressed, but this may be an indicator of an underlying problem of overlap between mechanisms by which different symptom clusters are associated with the cardiovascular system. The structure of the PCL includes both psychological symptoms as well as physical symptoms, such as problems with sleep and physical reactions to reminders of the trauma. Since these symptoms are also products of autonomic dysregulation (Stein and Pu, 2012), it might be that these items on the PCL produce endogeneity in models investigating PTSD and HRV. Additionally, bidirectionality may exist, whereby problems with sleep cause dysregulation in the autonomic system (reflected in HRV) and dysregulation in the autonomic system causes problems with sleep. Specific types of injuries, such as traumatic brain injuries, may have had additional effects on the autonomic system as measured by HRV (Talbert et al., 2024), but analysis of this outside the scope this current study. PTSD symptom duration may have varied in the cohort, but no data was available on index trauma, and so could not be controlled for. Lifestyle factors, such as exercise or alcohol/tobacco/illegal drug use, are likely to mediate the association between PTSD symptoms and autonomic functioning, which could not be taken into account in our analysis (Adams et al., 2020; Debell et al., 2014; Kearns et al., 2018; Whitworth et al., 2017). PTSD is a highly comorbid disorder, with 91.5 % of those with PTSD reporting mental health multimorbidity in this cohort (Dyball et al., 2022). As such, we were unable to control for the effects of depression or generalised anxiety. Rank was used as a proxy for socioeconomic status as no direct measures of socioeconomic status were available, meaning there may be some residual confounding in our models. Lastly, given the unavailability of ECG measurements at baseline, a surrogate source of HRV (via up to 16 s recording of pulse waveform) was used and only RMSSD was available. As the frequency-domain measures would have required longer recordings for accurate measurement (Kim et al., 2021), those could not be measured in this analysis. Nonetheless, the pulse waveform-derived ultra-short-term RMSSD (HRV) has been found to be as valid as the ECG-derived 5-min RMSSD (HRV) in our sample (Maqsood et al., 2024). It is anticipated that future investigation into the cohort will focus on the association between PTSD and other measures of short-term HRV.

5. Conclusions

Probable PTSD status was not associated with an indicator of HRV (RMSSD) in a cohort of UK military personnel who sustained serious physical combat injuries and demographically similar personnel without such injuries. However, symptoms of emotional numbing were associated with HRV. Different symptom clusters of PTSD may have unique

effects on the cardiovascular system, and symptom profiles may be associated with distinctive cardiovascular profiles.

Pre-registration

The ADVANCE study is ongoing and is registered with the ISRCTN registry, ISRCTN57285353.

CRediT authorship contribution statement

Daniel Dyball: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Rabeea Maqsood:** Writing – review & editing, Writing – original draft. **Susie Schofield:** Writing – review & editing, Methodology. **Alexander N. Bennett:** Writing – review & editing, Funding acquisition, Conceptualization. **Paul Cullinan:** Writing – review & editing, Funding acquisition, Conceptualization. **Anthony M.J. Bull:** Writing – review & editing, Funding acquisition, Conceptualization. **Christopher J. Boos:** Writing – review & editing, Funding acquisition, Conceptualization. **Nicola T. Fear:** Writing – review & editing, Funding acquisition, Conceptualization.

Ethics

The ADVANCE Study has full ethical approval from the UK 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.

Funding

The ADVANCE study is funded through the ADVANCE Charity. Key contributors to the charity are the Headley Court Charity (principal funder), HM Treasury (LIBOR Grant), Help for Heroes, Nuffield Trust for the Forces of the Crown, Forces in Mind Trust, National Lottery Community Fund, Blesma - The Limbless Vet-erans, the UK Ministry of Defence and the Office for Veterans' Affairs (OVA).

Declaration of competing interest

N.T.Fear is part funded by a grant from the UK Ministry of Defence and is and a trustee (unpaid) of a charity supporting the health and wellbeing of service personnel, veterans and their families. A.Bennett is a serving member of the Royal Air Force. The views expressed are those of the author(s) and not necessarily those of the Ministry of Defence.

Acknowledgements

We wish to thank all of the research staff at both Headley Court and Stanford Hall who helped with the ADVANCE study, including Maria-Benedicta Edwards, Helen Blackman, Melanie Chesnokov, Emma Coady, Sarah Evans, Guy Fraser, Meliha Kaya-Barge, Maija Maskuniitty, David Pernet, Helen Prentice, Urszula Pucilowska, Lalji Varsani, Anna Verey, Molly Waldron, Danny Weston, Tass White, Seamus Wilson, and Louise Young. For the purposes of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Accepted Author Manuscript version arising from this submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.01.087.

References

Adams, T.G., Forte, J., Fogle, B.M., Southwick, S.M., Pietrzak, R.H., 2020. Self-reported exercise frequency and PTSD: results from the National Health and resilience in veterans study. Acta Psychiatr. Scand. 142 (6), 486–495. https://doi.org/10.1111/acps.13234.

Alvares, G.A., Quintana, D.S., Hickie, I.B., Guastella, A.J., 2016. Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: a systematic review and meta-analysis. J. Psychiatry Neurosci. 41 (2), 89–104. https://doi.org/10.1503/jpn.140217.

Asmundson, G.J.G., Frombach, I., McQuaid, J., Pedrelli, P., Lenox, R., Stein, M.B., 2000. Dimensionality of posttraumatic stress symptoms: a confirmatory factor analysis of DSM-IV symptom clusters and other symptom models. Behav. Res. Ther. 38 (2), 203–214. https://doi.org/10.1016/S0005-7967(99)00061-3.

Bennett, A.N., Dyball, D.M., Boos, C.J., Fear, N.T., Schofield, S., Bull, A.M.J., Cullinan, P., 2020. Study protocol for a prospective, longitudinal cohort study investigating the medical and psychosocial outcomes of UK combat casualties from the Afghanistan war: the ADVANCE study. BMJ Open 10 (10), e037850. https://doi.org/10.1136/bmjopen-2020-037850.

Beutler, S., Mertens, Y.L., Ladner, L., Schellong, J., Croy, I., Daniels, J.K., 2022. Trauma-related dissociation and the autonomic nervous system: a systematic literature review of psychophysiological correlates of dissociative experiencing in PTSD patients. Eur. J. Psychotraumatol. 13 (2), 2132599. https://doi.org/10.1080/20008066.2022.2132599.

Billman, G.E., Huikuri, H.V., Sacha, J., Trimmel, K., 2015. An introduction to heart rate variability: methodological considerations and clinical applications [editorial]. Front. Physiol. 6. https://doi.org/10.3389/fphys.2015.00055.

Blanchard, E.B., Jones-Alexander, J., Buckley, T.C., Forneris, C.A., 1996. Psychometric properties of the PTSD checklist (PCL). Behav. Res. Ther. 34 (8), 669–673. https://doi.org/10.1016/0005-7967(96)00033-2.

Brudey, C., Park, J., Wiaderkiewicz, J., Kobayashi, I., Mellman, T.A., Marvar, P.J., 2015. Autonomic and inflammatory consequences of posttraumatic stress disorder and the link to cardiovascular disease. Am. J. Phys. Regul. Integr. Comp. Phys. 309 (4), R315–R321. https://doi.org/10.1152/ajpregu.00343.2014.

De Bin, R., Sauerbrei, W., 2018. Handling co-dependence issues in resampling-based variable selection procedures: a simulation study. J. Stat. Comput. Simul. 88 (1), 28–55.

Debell, F., Fear, N.T., Head, M., Batt-Rawden, S., Greenberg, N., Wessely, S., Goodwin, L., 2014. A systematic review of the comorbidity between PTSD and alcohol misuse. Soc. Psychiatry Psychiatr. Epidemiol. 49 (9), 1401–1425. https://doi.org/10.1007/s00127-014-0855-7.

Dyball, D., Evans, S., Boos, C.J., Stevelink, S.A., Fear, N.T., 2019. The association between PTSD and cardiovascular disease and its risk factors in male veterans of the Iraq/Afghanistan conflicts: a systematic review. Int. Rev. Psychiatry 31 (1), 34–48.

Dyball, D., Bennett, A.N., Schofield, S., Cullinan, P., Boos, C.J., Bull, A.M., Wessely, S., Stevelink, S.A., Fear, N.T., 2022. Mental health outcomes of male UK military personnel deployed to Afghanistan and the role of combat injury: analysis of baseline data from the ADVANCE cohort study. Lancet Psychiatry 9 (7), 547–554.

Dyball, D., Bennett, A.N., Schofield, S., Cullinan, P., Boos, C.J., Bull, A.M.J., Stevelink, S. A.M., Fear, N.T., 2023. The underlying mechanisms by which PTSD symptoms are associated with cardiovascular health in male UK military personnel: the ADVANCE cohort study. J. Psychiatr. Res. 159, 87–96. https://doi.org/10.1016/j.jpsychires.2023.01.010.

Fang, S.-C., Wu, Y.-L., Tsai, P.-S., 2020. Heart rate variability and risk of all-cause death and cardiovascular events in patients with cardiovascular disease: a meta-analysis of cohort studies. Biol. Res. Nurs. 22 (1), 45–56. https://doi.org/10.1177/1099800419877442.

Forster, G.L., Simons, R.M., Baugh, L.A., 2017. Revisiting the role of the amygdala in posttraumatic stress disorder. The amygdala-where emotions shape perception, learning and memories 67585.

Ge, F., Yuan, M., Li, Y., Zhang, W., 2020. Posttraumatic stress disorder and alterations in resting heart rate variability: a systematic review and Meta-analysis. Psychiatry Investig. 17 (1), 9–20. https://doi.org/10.30773/pi.2019.0112.

Hauschildt, M., Peters, M.J., Moritz, S., Jelinek, L., 2011. Heart rate variability in response to affective scenes in posttraumatic stress disorder. Biol. Psychol. 88 (2–3), 215–222. https://doi.org/10.1016/j.biopsycho.2011.08.004.

Heinze, G., Wallisch, C., Dunkler, D., 2018. Variable selection–a review and recommendations for the practicing statistician. Biom. J. 60 (3), 431–449.

Kearns, N.T., Carl, E., Stein, A.T., Vujanovic, A.A., Zvolensky, M.J., Smits, J.A.J., Powers, M.B., 2018. Posttraumatic stress disorder and cigarette smoking: a systematic review. Depress. Anxiety 35 (11), 1056–1072. https://doi.org/10.1002/da.22828.

Kim, J.W., Seok, H.S., Shin, H., 2021. Is ultra-short-term heart rate variability valid in non-static conditions? Front. Physiol. 12, 596060.

Lee, S.Y., Park, C.L., Cilhoroz, B.T., Pescatello, L.S., 2022. PTSD symptom clusters and cardiovascular responses to stress: reactivity and recovery. J. Psychosom. Res. 161, 110996. https://doi.org/10.1016/j.jpsychores.2022.110996.

Litz, B.T., Litz, B.T., Gray, M.J., 2002. Emotional numbing in posttraumatic stress disorder: current and future research directions. Australian & New Zealand Journal of Psychiatry 36 (2), 198–204. https://doi.org/10.1046/j.1440-1614.2002.01002.x.

Malik, M., 1996. Heart rate variability. Ann. Noninvasive Electrocardiol. 1 (2), 151–181. https://doi.org/10.1111/j.1542-474X.1996.tb00275.x.

Maqsood, R., Khattab, A., Bennett, A.N., Boos, C.J., 2023a. Reliability of carotid-femoral arterial waveforms for the derivation of ultra-short term heart rate variability in injured British servicemen: an inter-rater reliability study. PLoS One 18 (9), e0290618.

Maqsood, R., Schofield, S., Bennett, A.N., Bull, A.M., Fear, N.T., Cullinan, P., Khattab, A., Boos, C.J., 2023b. Relationship between combat-related traumatic injury and ultrashort term heart rate variability in a UK military cohort: findings from the ADVANCE study. *BMJ military*. Health e002316. https://doi.org/10.1136/military-2022-002316.

Maqsood, R., Schofield, S., Bennett, A.N., Khattab, A., Bull, A.M., Fear, N.T., Boos, C.J., 2024. Validity of ultra-short-term heart rate variability derived from femoral arterial pulse waveform in a British military cohort. Appl. Psychophysiol. Biofeedback 1–9.

Munoz, M.L., Van Roon, A., Riese, H., Thio, C., Oostenbroek, E., Westrik, I., de Geus, E.J., Gansevoort, R., Lefrandt, J., Nolte, I.M., 2015. Validity of (ultra-) short recordings for heart rate variability measurements. PLoS One 10 (9), e0138921.

Nagpal, M., Gleichauf, K., & Ginsberg, J. (2013). Meta-analysis of heart rate variability as a psychophysiological indicator of posttraumatic stress disorder. J. Trauma Treat., 3 (182), 2167-1222.1000182.

Nussinovitch, U., Elishkevitz, K.P., Katz, K., Nussinovitch, M., Segev, S., Volovitz, B., Nussinovitch, N., 2011. Reliability of ultra-short ECG indices for heart rate variability. Ann. Noninvasive Electrocardiol. 16 (2), 117–122. https://doi.org/10.1111/j.1542-474X.2011.00417.x.

Orini, M., van Duijvenboden, S., Young, W.J., Ramírez, J., Jones, A.R., Hughes, A.D., Tinker, A., Munroe, P.B., Lambiase, P.D., 2023. Long-term association of ultra-short heart rate variability with cardiovascular events. Sci. Rep. 13 (1), 18966. https://doi.org/10.1038/s41598-023-45988-2.

Park, J.E., Lee, J.Y., Kang, S.-H., Choi, J.H., Kim, T.Y., So, H.S., Yoon, I.-Y., 2017. Heart rate variability of chronic posttraumatic stress disorder in the Korean veterans. Psychiatry Res. 255, 72–77. https://doi.org/10.1016/j.psychres.2017.05.011.

Passos, I.C., Vasconcelos-Moreno, M.P., Costa, L.G., Kunz, M., Brietzke, E., Quevedo, J., Salum, G., Magalhães, P.V., Kapczinski, F., Kauer-Sant'Anna, M., 2015. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry 2 (11), 1002–1012.

Presciutti, A., Shaffer, J., Sumner, J.A., Elkind, M.S.V., Roh, D.J., Park, S., Claassen, J., Edmondson, D., Agarwal, S., 2020. Hyperarousal symptoms in survivors of cardiac arrest are associated with 13 month risk of major adverse cardiovascular events and all-cause mortality. Ann. Behav. Med. 54 (6), 413–422. https://doi.org/10.1093/abm/kaz058.

Pucci, G., Cheriyan, J., Hubsch, A., Hickson, S.S., Gajendragadkar, P.R., Watson, T., O'Sullivan, M., Woodcock-Smith, J., Schillaci, G., Wilkinson, I.B., McEniery, C.M., 2013. Evaluation of the Vicorder, a novel cuff-based device for the noninvasive estimation of central blood pressure. J. Hypertens. 31 (1), 77–85. https://doi.org/10.1097/HJH.0b013e32835a8eb1.

Rosenbaum, S., Stubbs, B., Ward, P.B., Steel, Z., Lederman, O., Vancampfort, D., 2015. The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: a systematic review and meta-analysis. Metabolism 64 (8), 926–933. https://doi.org/10.1016/j.metabol.2015.04.009.

Sauerbrei, W., Perperoglou, A., Schmid, M., Abrahamowicz, M., Becher, H., Binder, H., Dunkler, D., Harrell, F.E., Royston, P., Heinze, G., 2020. State of the art in selection of variables and functional forms in multivariable analysis—outstanding issues. Diagnostic and prognostic research 4, 1–18.

Schneider, M., Schwerdtfeger, A., 2020. Autonomic dysfunction in posttraumatic stress disorder indexed by heart rate variability: a meta-analysis. Psychol. Med. 50 (12), 1937–1948. https://doi.org/10.1017/S003329172000207X.

Schuman, D.L., Killian, M.O., 2019. Pilot study of a single session heart rate variability biofeedback intervention on veterans' posttraumatic stress symptoms. Appl. Psychophysiol. Biofeedback 44 (1), 9–20. https://doi.org/10.1007/s10484-018-9415-3.

Shaffer, F., Ginsberg, J.P., 2017. An overview of heart rate variability metrics and norms [review]. Front. Public Health 5. https://doi.org/10.3389/fpubh.2017.00258.

Stein, P.K., Pu, Y., 2012. Heart rate variability, sleep and sleep disorders. Sleep Med. Rev. 16 (1), 47–66. https://doi.org/10.1016/j.smrv.2011.02.005.

Steptoe, A., Feldman, P.J., Kunz, S., Owen, N., Willemsen, G., Marmot, M., 2002. Stress responsivity and socioeconomic status. A mechanism for increased cardiovascular disease risk? Eur. Heart J. 23 (22), 1757–1763.

Talbert, L.D., Kaelberer, Z., Gleave, E., et al., 2024. A systematic review of the relationship between traumatic brain injury and disruptions in heart rate variability. Appl. Psychophysiol. Biofeedback. https://doi.org/10.1007/s10484-024-09663-.

Tan, G., Dao, T.K., Farmer, L., Sutherland, R.J., Gevirtz, R., 2011. Heart rate variability (HRV) and posttraumatic stress disorder (PTSD): a pilot study. Appl. Psychophysiol. Biofeedback 36 (1), 27–35. https://doi.org/10.1007/s10484-010-9141-y.

Tawakol, A., Ishai, A., Takx, R.A., Figueroa, A.L., Ali, A., Kaiser, Y., Truong, Q.A., Solomon, C.J., Calcagno, C., Mani, V., Tang, C.Y., Mulder, W.J., Murrough, J.W., Hoffmann, U., Nahrendorf, M., Shin, L.M., Fayad, Z.A., Pitman, R.K., 2017. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet 389 (10071), 834–845. https://doi.org/10.1016/s0140-6736(16)31714-7.

Thong, T., Li, K., McNames, J., Aboy, M., & Goldstein, B. (2003). Accuracy of ultra-short heart rate variability measures. Proceedings of the 25th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (IEEE Cat. No. 03CH37439).

Van Ginkel, J.R., Andries Van der Ark, L., Sijtsma, K., Vermunt, J.K., 2007. Two-way imputation: a Bayesian method for estimating missing scores in tests and questionnaires, and an accurate approximation. Computational Statistics & Data Analysis 51 (8), 4013–4027. https://doi.org/10.1016/j.csda.2006.12.022.

Voss, A., Schroeder, R., Heitmann, A., Peters, A., Perz, S., 2015. Short-term heart rate variability—influence of gender and age in healthy subjects. PLoS One 10 (3), e0118308. https://doi.org/10.1371/journal.pone.0118308.

Weathers, F. W., Litz, B. T., Herman, D. S., Huska, J. A., & Keane, T. M. (1993, October). The PTSD checklist (PCL): Reliability, validity, and diagnostic utility. In *Annual Convention of the International Society for Traumatic Stress Studies,* San Antonio, TX (Vol. vol. 462).

Whitworth, J.W., Craft, L.L., Dunsiger, S.I., Ciccolo, J.T., 2017. Direct and indirect effects of exercise on posttraumatic stress disorder symptoms: a longitudinal study. Gen. Hosp. Psychiatry 49, 56–62.

World Health Organisation Collaboration Centre for Drug Statistics Methodology, 2020. ATC Classification Index with DDDs 2020. Oslo, Norway.

Yoong, S., Miles, D., McKinney, P., Smith, I., Spencer, N., 1999. A method of assigning socio-economic status classification to British Armed Forces personnel. J. R. Army Med. Corps 145 (3), 140–142.