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Association between combat-related traumatic injury and cardiovascular risk

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ABSTRACT

Objective The association between combat-related traumatic injury (CRTI) and cardiovascular risk is uncertain. This study aimed to investigate the association between CRTI and both metabolic syndrome (MetS) and arterial stiffness.

Methods This was a prospective observational cohort study consisting of 579 male adult UK combat veterans (UK-Afghanistan War 2003–2014) with CRTI who were frequency-matched to 565 uninjured men by age, service, rank, regiment, deployment period and role-in-theatre. Measures included quantification of injury severity (New Injury Severity Score (NISS)), visceral fat area (dual-energy X-ray absorptiometry), arterial stiffness (heart rate-adjusted central augmentation index (cAIx) and pulse wave velocity (PWV)), fasting venous blood glucose, lipids and high-sensitivity C reactive protein (hs-CRP).

Results Overall the participants were 34.1±5.4 years, with a mean (±SD) time from injury/deployment of 8.3±2.1 years. The prevalence of MetS (18.0% vs 11.8%; adjusted risk ratio 1.46, 95% CI 1.10 to 1.94, p<0.0001) and the mean cAIx (17.61%±8.79% vs 15.23%±8.19%, p<0.0001) were higher among the CRTI versus the uninjured group, respectively. Abdominal waist circumference, visceral fat area, triglycerides, estimated insulin resistance and hs-CRP levels were greater and physical activity and high-density lipoprotein-cholesterol lower with CRTI. There were no significant between-group differences in blood glucose, blood pressure or PWV. CRTI, injury severity (↑NISS), age, socioeconomic status (SEC) and physical activity were independently associated with both MetS and cAIx.

Conclusions CRTI is associated with an increased prevalence of MetS and arterial stiffness, which are also influenced by age, injury severity, physical activity and SEC. The longitudinal impact of CRTI on clinical cardiovascular events needs further examination.

INTRODUCTION

The long-term health outcomes of survivors of combat-related traumatic injury (CRTI) are unclear. It has been reported that severe CRTI may be associated with an increased risk of cardiovascular disease (CVD) and major adverse cardiovascular events (MACE).[1–3] However, a recent systematic review and meta-analysis has shown that the strength of this evidence is modest, at best, and derived from retrospective studies relating to injuries sustained ≥40 years ago or from small cross-sectional studies with poorly defined control groups.[4] There is a need for a contemporary prospective cohort study examining the relationship between CRTI and its severity to earlier markers of cardiovascular risk, which if established would prompt prevention strategies to mitigate the risk.[5]

Metabolic syndrome (MetS) and arterial stiffness are two recognised markers of cardiovascular risk. MetS affects up to 30% of Western adults, with a prevalence that is rapidly rising.[6] MetS is associated with increased arterial stiffness and MACE.[7 8] Among the measures of arterial stiffness, pulse wave velocity (PWV) remains the gold standard. However, there is increasing interest in central augmentation index (cAIx), which may be a more sensitive marker of early arterial stiffness and endothelial dysfunction.[9 10] Moreover, increased cAIx has been linked to all-cause mortality and MACE. Two recent studies have reported an association between CRTI and MetS.[11 12] They were both retrospective and did not include an uninjured comparison group. The relationship between CRTI and arterial stiffness has not been examined.

The ADVANCE (ArmeD SerVices TrAuma RehabilitatioN OutComE) study seeks to address these knowledge gaps in a contemporary population with CRTI. This baseline analysis of the ADVANCE cohort aimed to investigate, for the first time, the relationship between CRTI, MetS and arterial stiffness.

METHODS

Study design

The ADVANCE study is a prospective cohort study designed to investigate the long-term health outcomes of British combat casualties who sustained CRTI during recent military operations in Afghanistan (2003–2014). Details of the study design, sampling and protocol have been previously published.[5] The primary outcomes were the relative prevalence of MetS and large artery stiffness (using cAIx) among injured versus uninjured servicemen.

Study population

Between March 2016 and August 2020, male UK military personnel (≥18 years) who had sustained CRTI (sufficient to require aeromedical evacuation) were compared with a frequency-matched comparison group (by age, service, rank, regiment, deployment period and role-in-theatre) of

Table 1 Baseline demographics among uninjured versus CRTI participants

	Uninjured vs CRTI			CRTI by NISS category		
	Uninjured	CRTI	P value†	NISS <13	NISS ≥13	P value‡
Number	565	579	–	288	291	–
Age at sampling, years	26.02±5.07	25.71±5.16	0.31	25.82±5.45	25.61±4.87	0.53
Age at assessment, years	34.24±5.41	34.01±5.35	0.49	34.49±5.48	33.54±5.18	0.08
Time from deployment/injury to assessment, years	8.2±2.15	8.33±2.14	0.36	8.70±2.08	7.96±2.15	0.0001§¶
Still serving in military	454 (80.4)	159 (27.5)	<0.0001	110 (38.2)	49 (16.8)	<0.0001
Rank/NS-SEC (at sampling)						
Senior rank (NS-SEC 1)	79 (14.0)	60 (10.4)	<0.001	28 (9.7)	32 (11.0)	0.20
Mid-rank (NS-SEC 2)	147 (26.0)	106 (18.3)		61 (21.2)	45 (15.5)	
Lower rank (NS-SEC 3)	339 (60.0)	413 (71.3)		199 (69.1)	214 (73.5)	
Injury mechanism						0.010
Blast	–	435 (75.1)	–	201 (69.8)	234 (80.4)	
On-blast (accidents, gunshot, burns)	–	144 (24.9)	–	87 (30.2)	57 (19.6)	
Injury type: limb amputation	–	161 (27.8)		17 (5.9)	144 (49.5)	<0.0001
NISS, median (IQR)	–	13.0 (5.0–30.0)	–	5.0 (3.0–9.0)	29.0 (20.0–45.0)	<0.0001
Ethnicity: Caucasian	512 (90.6)	525 (90.6)	1.0	259 (89.9)	265 (91.1)	0.75
Family history of CVD*	111 (19.6)	106 (18.3)	0.60	53 (18.4)	53 (18.28)	0.85
Smoking history						0.37
Current smoker	126 (22.3)	119 (20.6)		66 (22.9)	53 (18.2)	
Ex-smoker	178 (31.5)	168 (29.0)	–	84 (29.2)	84 (28.9)	
Never	261 (46.2)	292 (50.4)	0.36	138 (47.9)	154 (52.9)	

Data presented as mean±SD or number (%) unless otherwise stated.
*Defined as history of stroke of confirmed coronary heart disease in one or more first-degree relative.
†Tests the difference between CRTI and uninjured.
‡Tests the difference between uninjured (where applicable), NISS <13 and NISS ≥13.
§Significant (p<0.05) post-hoc differences: uninjured vs NISS <13.
¶Significant (p<0.05) post-hoc differences: NISS <13 vs NISS ≥13.
CRTI, combat-related traumatic injury; CVD, cardiovascular disease; NISS, New Injury Severity Score; NS-SEC, National Statistics Socio-Economic Classification.

uninjured servicemen. Identification and sampling of the injured and uninjured groups were undertaken by the Defence Statistics (Health) within the UK Ministry of Defence using deployment and medical records.

Participants with established CVD (history of stroke or transient ischaemic attack, ischaemic heart disease (IHD), peripheral vascular disease) prior to their injury/deployment of interest or evidence of active acute infection at baseline survey were excluded.[5]

Patients and the public were engaged, and continue to be so, in the study design, research questions, outcome measures, conduct and logistics of the study via focus groups, feedback questionnaires, newsletters and via the ADVANCE study website (https://www.advancestudydmrc.org.uk). Study participation was voluntary and following full informed consent.

Biometric data and blood tests

Prior to the baseline study visit, participants were asked to fast and refrain from caffeine and alcohol for at least 8 hours. Questionnaires were completed during a clinical interview with a trained research nurse; data included confirmation of the participant's ethnicity, medical and family history (of stroke or IHD) and smoking status. Baseline measures included height, body mass and abdominal waist circumference (AWC) measured manually. For men with amputations, we adjusted the body weight (and hence body mass index) using an established correction formula to account for the mass of their missing limb(s).[13]

Blood glucose, glycated haemoglobin (HbA1c), lipid level, high-sensitivity C reactive protein (hs-CRP; lower detection limit 0.10 mg/L) and full blood count were measured in venous blood processed by the local hospital laboratory.

Diagnosis of MetS and assessment of insulin resistance

The presence of MetS was established (binary yes/no) in accordance with the American Heart Association criteria of three out of the following five: (1) central obesity (AWC ≥102 cm), (2) triglycerides ≥1.7 mmol/L, (3) high-density lipoprotein (HDL)-cholesterol <1.03 mmol/L, (4) blood pressure ≥130/85 mm Hg (or treated for hypertension) and (5) fasting plasma glucose ≥5.6 mmol/L.[7]

Insulin resistance was assessed using the estimated glucose disposal rate (eGDR) calculated as the following: eGDR mg/kg/min=21.158+(−0.09×AWC (cm))+(−3.407×hypertension (yes=1, no=0))+(−0.551×HbA1c %).[14] A lower eGDR is indicative of greater relative insulin resistance.[14]

Assessment of injury severity and socioeconomic class

The severity of the original CRTI was quantified using the New Injury Severity Score (NISS),[15] provided by the UK Joint Theatre Trauma Registry, which is a prospectively collected database of every service casualty admitted to a deployed UK medical facility.[5]

Socioeconomic status (SEC) was classified by military rank at the time of deployment using the three-tier National Statistics Socio-Economic Classification (NS-SEC): senior rank (commissioned officers), NS-SEC group 1; mid-rank (senior non-commissioned officers), NS-SEC group 2; and junior rank

Table 2 Comparative anthropometric indices and venous blood results of uninjured versus CRTI participants

	Uninjured vs CRTI			CRTI by NISS category		
	Uninjured	CRTI	P value*	NISS <13	NISS ≥13	P value†
Height, cm	178.8±6.4	179.3±7.1	0.25	179.0±6.8	1.79±0.07	0.25
Body mass, kg	87.85±12.24	90.56±14.38	0.0006	90.39±14.45	90.39±14.34	0.003‡§
Waist circumference, cm	93.48±9.97	95.72±10.17	0.0002	95.78±10.40	95.89±10.17	0.001‡§
Visceral fat area, cm^2	83.0 (66.5–108.5)	91.0 (70.0–120.0)	0.0002	89.0 (69.0–120.0)	93.23 (71.0–122.8)	0.008‡§
Haemoglobin, g/L	152.40±8.77	152.10±9.83	0.68	152.2±8.73	152.0±10.80	0.90
Platelet count, $\times 10^9$/L	234.0±45.10	241.4±60.43	0.02	237.6±49.56	245.0.3±69.39	0.02§
White cell count, $\times 10^9$/L	5.58±1.35	5.74±1.73	0.07	5.59±1.47	5.89±1.94	0.01§
hs-CRP, mg/L	0.85 (0.50–1.76)	1.02 (0.50–2.10)	0.02	0.88 (0.47–1.81)	1.20 (0.50–2.50)	0.008§¶
Total cholesterol, mmol/L	5.02±0.97	4.93±0.99	0.09	4.96±0.97	4.89±1.02	0.16
HDL-cholesterol, mmol/L	1.31±0.30	1.26±0.32	0.005	1.31±0.33	1.21±0.31	<0.0001§¶
Triglycerides, mmol/L	1.30±0.94	1.40±0.95	0.02	1.36±0.77	1.43±1.08	0.08
Glucose, mmol/L	4.95±0.66	5.01±1.32	0.43	5.00±1.29	5.00±1.35	0.73
HbA1c, mmol/mol	34.60±3.79	34.72±8.35	0.76	34.68±8.61	34.76±8.09	0.94
eGDR, mg/kg/min	10.21±0.93	9.98±1.08	0.0002	10.01±1.08	9.96±1.08	0.008‡§
Metabolic syndrome, n (%)	66/558 (11.8)	102/567 (18.0)	0.004	43/282 (15.2)	59/285 (20.7)	0.003

*Tests the difference between CRTI and uninjured.
†Tests the difference between uninjured, NISS <13 and NISS ≥13.
‡Significant (p<0.05) post-hoc difference: uninjured vs NISS <13.
§Significant (p<0.05) post-hoc difference: uninjured vs NISS ≥13.
¶Significant (p<0.05) post-hoc difference: NISS <13 vs NISS ≥13.
CRTI, combat-related traumatic injury; eGDR, estimated glucose disposal rate; HBA1c, glycated haemoglobin; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; NISS, New Injury Severity Score.

(junior non-commissioned officers and other lower ranks), NS-SEC group 3.[16 17]

Body composition assessment and physical fitness

Visceral fat area was measured using dual-energy X-ray absorptiometry (Vertec Horizon and Discovery, UK).[5] Total weekly leisure time physical activities were quantified using the International Physical Activity Questionnaire and graded according to the WHO weekly recommendation of ≥150 min of moderate and/or >75 min of vigorous exercise.[18 19] Physical function was measured using the 6 min walk distance (6MWD) test.[5]

Measurement of arterial stiffness and blood pressure

Arterial stiffness and central blood pressures were measured using a Vicorder device (Skidmore Medical, UK).[20] Measurements were undertaken by trained research nurses in a

Table 3 Comparative haemodynamic and exercise data between uninjured and CRTI participants

	Uninjured vs CRTI			CRTI by NISS category		
Characteristics	Uninjured	CRTI	P value¶	NISS <13	NISS ≥13	P value**
Heart rate, per minute	56.27±8.38	59.91±9.99	<0.0001	58.48±9.30	61.32±10.47	<0.0001††‡‡§§
Brachial systolic blood pressure, mm Hg	132.0±11.44	131.0±11.47	0.14	131.9±10.79	130.1±12.04	0.06
Brachial diastolic blood pressure, mm Hg	2.06±8.25	71.79±8.81	0.60	71.28±8.62	72.29±8.97	0.31
Mean brachial arterial pressure, mm Hg	94.68±9.68	94.69±9.81	0.99	94.83±9.39	94.59±10.22	0.96
Aortic systolic blood pressure, mm Hg	127.2±11.88	126.6±11.74	0.37	127.2±11.14	125.9±12.29	0.30
Central augmentation index, %*	15.20±8.20	17.59±8.77	<0.0001	17.04±8.56	18.18±8.98	<0.0001††‡‡
Pulse wave velocity, m/s	8.11±1.61	8.23±1.95	0.26	8.32±1.86	8.14±2.04	0.26
Stroke volume index, mL/m^2†	55.47±10.79	53.10±11.33	0.003	54.39±11.12	51.83±11.49	<0.0001‡‡§§
Cardiac index, L/m^2‡	3.10±0.63	3.14±0.68	0.25	3.15±0.68	3.13±0.69	0.43
Physical activity recommendation, %§	351/536 (65.5)	315/548 (57.5)	0.007	157/279 (56.3)	158/269 (58.7)	0.022
6 min walk distance, m	630.6±95.69	538.1±173.8	<0.0001	592.5±136.1	484.1±189.9	<0.0001††‡‡§§

Data presented as mean (SD), median (IQR) or number (%), unless otherwise stated.
All physiological parameters were obtained using the Vicorder device.
*Corrected for resting heart rate.
†Calculated as the stroke volume divided by body surface area.
‡Calculated as SVI×resting heart rate.
§Defined as >150 min of moderate or >75 min of vigorous weekly physical exercise.
¶Tests the difference between CRTI and uninjured.
**Tests the difference between uninjured, NISS <13 and NISS ≥13.
††Significant (p<0.05) post-hoc differences: uninjured vs NISS <13.
‡‡Significant (p<0.05) post-hoc differences: uninjured vs NISS ≥13.
§§Significant (p<0.05) post-hoc differences: NISS <13 vs NISS ≥13.
CRTI, combat-related traumatic injury; NISS, New Injury Severity Score; SVI, stroke volume index.

Table 4 Comparative prevalence of metabolic syndrome defining criteria (yes/no) in relation to CRTI and injury severity (NISS)

	Uninjured vs injured			Injury by NISS		
Characteristics	Uninjured (n=565) n (%)	Injured (n=579) n (%)	P value*	NISS <13 (n=288) n (%)	NISS ≥13 (n=291) n (%)	P value†
Waist circumference >103 cm	115/565 (20.4)	166/579 (28.7)	0.001	79/288 (27.4)	87/291 (29.9)	0.004
High-density lipoprotein <1.03 mmol/L	98/560 (17.5)	148/568 (26.1)	0.005	57/283 (20.1)	91/285 (31.9)	<0.0001
Triglycerides >1.7 mmol/L	114/561 (20.3)	149/568 (26.2)	0.02	70/283 (24.7)	79/285 (27.7)	0.04
Fasting glucose >5.6 mmol/L	43/532 (8.1)	49/554 (8.8)	0.61	28/275 (10.2)	21/279 (7.5)	0.50
Blood pressure >130/85 mm Hg	303/564 (52.7)	290/577 (50.2)	0.26	157/287 (54.7)	133/290 (45.9)	0.05

χ^2 results are presented.
*Tests the difference between CRTI and uninjured.
†Tests the difference between uninjured, NISS <13 and NISS ≥13.
CRTI, combat-related traumatic injury; NISS, New Injury Severity Score.

temperature-controlled room after the participants had rested for 5 min, lying supine with their head raised to 30°.

Arterial stiffness was quantified using PWV and cAIx. Following measurement of brachial blood pressure, brachial arterial pulse waveform analysis at diastolic blood pressure was used to estimate central augmentation and systolic blood pressure, cAIx, stroke volume index (SVI, stroke volume ÷ body surface area), and cardiac index (SVI × heart rate).[20] Body surface area was calculated as the square root of the following: height (cm) multiplied by weight (kg) divided by 3600. The cAIx (central augmentation pressure ÷ central pulse pressure, %) was adjusted to resting heart rate as previously described.[21] All Vicorder measures were done in triplicate, with the average value used.

Table 5 Demographics and biomarkers by presence or absence of metabolic syndrome

	Metabolic syndrome		
	No (n=976)	Yes (n=168)	P value*
Age at assessment, years	33.89±5.27	35.50±5.78	0.0003
Rank/NS-SEC (at sampling), n (%)			
Senior rank (NS-SEC 1)	129 (13.2)	10 (5.9)	0.03
Mid-rank (NS-SEC 2)	213 (21.8)	40 (23.8)	
Junior rank (NS-SEC 3)	634 (65.0)	118 (70.2)	
Caucasian, n (%)	881/976 (90.2)	155/168 (92.3)	0.48
Time from exposure/injury, years	8.28±2.17	8.19±2.0	0.60
Physical activity recommendation†, n (%)	598/927 (64.5)	68/157 (43.3)	<0.0001
6 min walk distance	594.6±139.40	520.61±179.20	<0.0001
eGDR, mg/kg/min	10.30±0.85	8.92±1.10	<0.0001
hs-CRP, mg/L	0.80 (0.45–1.70)	1.73 (1.0–3.60)	<0.0001
New Injury Severity Score‡	12.0 (5.0–29.0)	22.0 (6.0–41.0)	0.012
Heart rate, min	57.09±8.79	64.05±10.63	<0.0001
Brachial systolic blood pressure, mm Hg	130.3±10.96	138.7±11.67	<0.0001
Aortic systolic blood pressure, mm Hg	125.4±11.20	135.5±11.54	<0.0001
Central augmentation index, %	15.43±8.45	22.1±6.92	<0.0001
Pulse wave velocity, m/s	8.13±1.82	8.38±1.60	0.010

*Tests the difference between those with and without metabolic syndrome.
†>150 min of moderate or >75 min of vigorous recreational physical exercise per week.
‡Only applies to the injured portion of the cohort.
eGDR, estimated glucose disposal rate; hs-CRP, high-sensitivity C reactive protein; NS-SEC, National Statistics Socio-Economic Classification.

Statistical analysis

Continuous data were presented as mean (SD), or where their distribution was skewed by median (IQR). Unpaired t-test or Mann-Whitney U test, as appropriate, was used in two-group comparisons of continuous data; three-group comparisons were made using one-way analysis of variance or Kruskal-Wallis test with Tukey and Dunn post-hoc tests, respectively. χ^2 or Fisher's exact tests were used to compare categorical data. Correlations were measured using Pearson or Spearman rank coefficients (95% CI) for continuous variables.

The relationship between CRTI (yes/no), its severity (NISS) and cAIx was examined using multivariable linear regression analyses. Plots of the residuals were visually inspected and variance inflation factors checked to assess model fit and any violation of assumptions. A modified Poisson regression (with a robust error variance) was used to estimate risk ratio (RR) and 95% CI to assess the association between CRTI (yes/no), CRTI severity and MetS (which is recommended when events are common; >10%).[22] The influence of injury severity was investigated using the median NISS.

Given their recognised associations with MetS and cAIx, we adjusted, a priori, for the following pre-exposure confounders:

Table 6 Correlations between variables and central augmentation index

	Central augmentation index	
	Correlation coefficient (95% CI)	P value
Age	0.22 (0.16 to 0.28)	<0.0001
6 min walk distance, m	−0.17 (−0.23 to −0.12)	<0.0001
Abdominal waist circumference	0.40 (0.35 to 0.45)	<0.0001
Visceral fat, %	0.48 (0.44 to 0.53)	<0.0001
Total cholesterol, mmol/L	0.14 (0.08 to 0.20)	<0.0001
Triglycerides, mmol/L	0.34 (0.28 to 0.39)	<0.0001
HDL-cholesterol, mmol/L	−0.23 (−0.29 to −0.18)	<0.0001
Glucose, mmol/L	0.20 (0.14 to 0.26)	<0.0001
eGDR, mg/kg/min	−0.40 (−0.45 to 0.035)	<0.0001
hs-CRP, mg/L	0.26 (0.20 to 0.31)	<0.0001
Brachial systolic blood pressure, mm Hg	0.23 (0.17 to 0.28)	<0.0001
Brachial diastolic blood pressure, mm Hg	0.13 (0.08 to 0.19)	<0.0001
Aortic systolic blood pressure, mm Hg	0.35 (0.30 to 0.40)	<0.0001
Pulse wave velocity, m/s	0.09 (0.03 to 0.14)	0.004

eGDR, estimated glucose dispersion rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein.

Table 7 Results of regression analyses of metabolic syndrome and central augmentation index with combat-related traumatic injury, by injured/uninjured (model 1) and by injury severity (model 2)

	Univariable		Model 1		Model 2	
Metabolic syndrome (yes/no)						
	Unadjusted RR (95% CI)	P value	Adjusted RR (95% CI)	P value	Adjusted RR (95% CI)	P value
Uninjured (ref)	(ref)		(ref)	–	–	–
Injured	1.52 (1.14 to 2.02)	0.005	1.34 (1.10 to 1.79)	0.045	–	–
Uninjured (ref)	(ref)	–	–	–	(ref)	–
Injured (NISS <13)	1.28 (0.90 to 1.83)	0.17	–	–	1.17 (0.82 to 1.67)	0.39
Injured (NISS ≥13)	1.74 (1.26 to 2.40)	0.001	–	–	1.53 (1.10 to 2.12)	0.01
Age at assessment, years	1.04 (1.02 to 1.07)	<0.0001	1.07 (1.04 to 1.1)	<0.0001	1.08 (1.04 to 1.10)	<0.0001
Time from injury, years	0.99 (0.93 to 1.05)	0.65	0.93 (0.87 to 1.00)	0.051	0.94 (0.88 to 1.00)	0.07
Physical activity	0.48 (0.36 to 0.64)	<0.0001	0.52 (0.39 to 0.70)	<0.0001	0.89 (0.27 to 2.87)	0.84
NS-SEC/rank, at sampling						
Senior rank (NS-SEC 1)	(ref)	–	(ref)	–	(ref)	–
Mid-rank (NS-SEC 2)	2.22 (1.15 to 4.29)	0.02	2.16 (1.10 to 4.27)	0.03	2.17 (1.10 to 4.26)	0.03
Junior rank (NS-SEC 3)	2.21 (1.19 to 4.12)	0.01	2.91 (1.50 to 6.64)	<0.002	2.91 (1.51 to 5.62)	0.001
Ethnicity (Caucasian)	1.22 (0.72 to 2.07)	0.47	1.83 (0.99 to 3.35)	0.052	1.83 (1.0 to 3.34)	0.051
Heart rate-adjusted central augmentation index, %						
Uninjured (ref)	(ref)	–	(ref)	–	–	–
Injured	2.37 (1.38 to 3.35)	<0.0001	1.89 (0.93 to 2.86)	<0.0001	–	–
Uninjured (ref)	(ref)	–	–	–	(ref)	–
Injured (NISS <13)	1.80 (0.60 to 3.01)	0.003	–	–	1.22 (0.04 to 2.39)	0.04
Injured (NISS ≥13)	2.94 (1.74 to 4.15)	<0.0001	–	–	2.59 (1.40 to 3.78)	<0.0001
Age at assessment, years	0.31 (0.22 to 0.40)	<0.0001	0.42 (0.31 to 0.53)	<0.0001	0.42 (0.31 to 0.53)	<0.0001
Time from injury, years	0.30 (0.07 to 0.54)	0.010	−0.02 (−0.27 to 0.22)	0.85	−0.002 (−0.25 to 0.24)	0.99
Physical activity	−3.12 (−4.15 to −2.10)	<0.0001	−2.37 (3.37 to 1.37)	<0.0001	−2.38 (−3.38 to −1.38)	<0.0001
NS-SEC/rank, at sampling						
Senior rank (NS-SEC 1)	(ref)	–	(ref)	–	(ref)	–
Mid-rank (NS-SEC 2)	4.34 (−0.03 to 2.36)	<0.0001	3.58 (1.87 to 5.28)	<0.0001	3.62 (1.92 to 5.33)	<0.0001
Junior rank (NS-SEC 3)	3.76 (2.58 to 6.10)	<0.0001	4.78 (3.18 to 6.38)	<0.0001	4.78 (3.18 to 6.37)	<0.0001
Ethnicity, Caucasian	−2.34 (−4.05 to −0.64)	0.007	−1.08 (−2.80 to 0.64)	0.22	−1.09 (−2.81 to 0.63)	0.21

NISS, New Injury Severity Score; NS-SEC, National Statistics Socio-Economic Classification; ref, reference; RR, risk ratio (from Poisson models with a robust variance).

age, ethnicity (Caucasian vs non-Caucasian) and SEC.[18 23] Injury severity, physical activity and time from injury/deployment were also adjusted for in order to allow for any systematic differences in this variable.

Multiple imputation methods were not used as there were very few (<5%) missing data and complete case analyses were undertaken. Sensitivity analyses (not shown) to take account of weights were performed. First a sample weight was calculated to take account of undersampling of the less severely injured group. Then a response weight was calculated to take account of non-response, calculated as the inverse probability of responding based on age, rank and service. An overall weight was derived (sample-weight multiplied by response-weight) and analyses were conducted using the svy command in Stata V.17. The results were similar and therefore only the unweighted analyses were reported.

A two-tailed p<0.05 was considered statistically significant. Statistical analyses were undertaken with SPSS V.26.0 and GraphPad Prism V.6.07 for Windows (GraphPad Software, San Diego, California, USA).

RESULTS

Description of the study population

The final sample comprised 1144 men (579 with CRTI, 50.6%) with a mean age of 26.1±5.2 years at the time of their injury or relevant deployment and 34.1±5.4 years at baseline assessment. The mean time from injury/deployment was 8.3±2.1 years. The adjusted response rates (excluding those who had died, had no known contact details or for whom no contact was attempted) were 59.6% and 56.3% for the injured and the uninjured group, respectively (p=0.56). The respondents in each group were similar in terms of age, ethnicity, height, family history of CVD, smoking history and time from deployment/injury to assessment (table 1). Compared with the uninjured group, the CRTI group were less likely to be still serving and were of lower SEC/rank (table 1). For those in the CRTI group, blast was the most common mechanism of injury, followed by gunshot wounds and other causes (eg, vehicular accidents, falls, etc). There were 161 men (27.8% of the CRTI group) with limb amputations (table 1). The median NISS was 13.0 (IQR, 5.0–30.0), with scores ranging from 1 to 75 (online supplemental figure 1). Among the CRTI group there were 288 participants with an NISS of <13 and 291 with an NISS of ≥13. The proportions of amputees and participants with blast injury were both greater in those with higher (NISS ≥13) than lower (NISS <13) trauma scores.

Venous blood, physiological and metabolic measurements

Adjusted body mass, AWC, visceral fat area, hs-CRP, triglycerides, platelet count, resting heart rate and cardiac index were significantly higher whereas HDL-cholesterol, eGDR, SVI, 6MWD and physical activity were lower in those in the CRTI group (tables 2 and 3). The prevalence of MetS (18.0% vs 11.8%; adjusted RR, 1.48, 95% CI 1.09 to 1.34, p<0.0001) and cAIx (17.61%±8.79% vs 15.23%±8.19%, p<0.0001) was higher

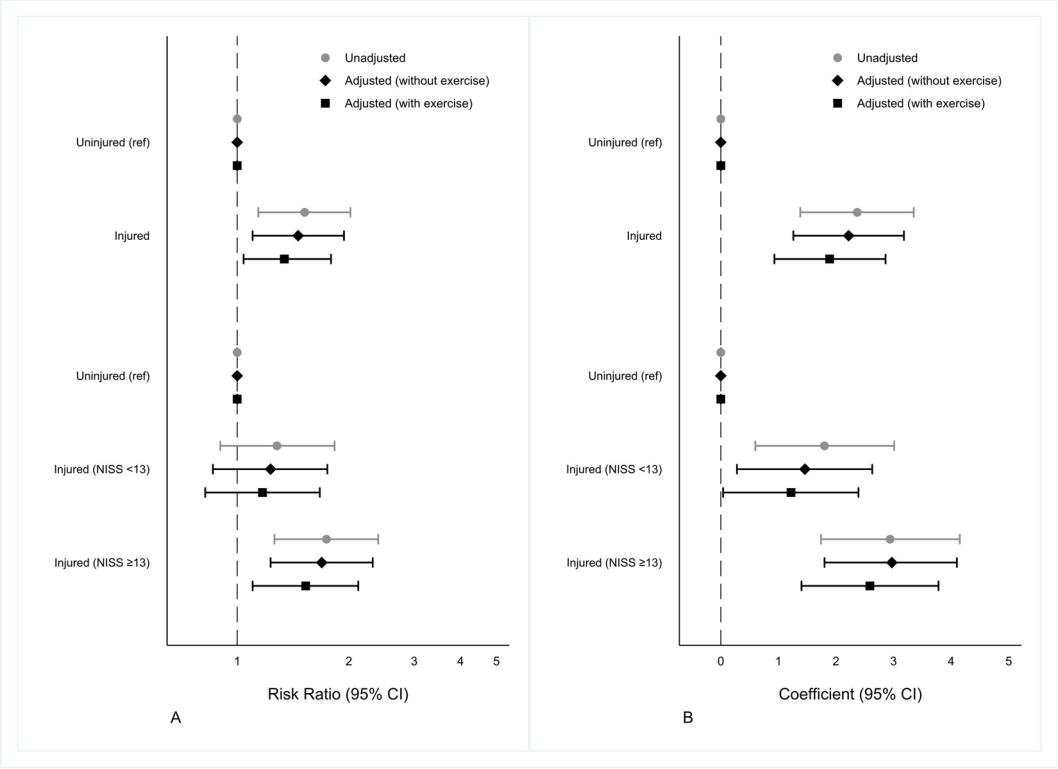

Figure 1 Results of regression analyses of (A) metabolic syndrome and (B) central augmentation index with combat-related traumatic injury, by injured/uninjured and by injury severity. The figure shows unadjusted, adjusted (excluding exercise) and adjusted (including exercise) risk ratios and regression coefficients and their 95% CI. NISS, New Injury Severity Score; ref, reference.

among the CRTI group versus the uninjured group. The prevalence of MetS and cAIx was significantly higher with worsening injury severity (tables 2 and 3). There were no significant differences in fasting blood glucose, white cell count, HbA1c, blood pressure and PWV between the two groups. The number of participants with AWC, triglyceride and HDL-cholesterol values that fulfilled the defining criteria for MetS was higher in the CRTI group (table 4).

Relationship between cAIx, MetS and cardiovascular risk factors

eGDR, achieved physical activity recommendation and 6MWD were lower whereas age, NISS, hs-CRP, heart rate, brachial and central systolic blood pressure, cAIx and proportion of lower ranks (NS-SEC 2 and 3) were higher in participants with MetS versus those without MetS (table 5).

Age, AWC, visceral fat, triglycerides, hs-CRP, brachial systolic and both diastolic blood pressure and aortic systolic blood pressure all positively correlated with cAIx; HDL-cholesterol, eGDR and 6MWD were inversely correlated (table 6).

Association between traumatic injury, MetS and cAIx

Regression analyses revealed significant associations between CRTI and both MetS and cAIx that were independent not only of age, ethnicity, SEC and time since injury/deployment, but also physical activity (table 7 and figure 1). For each outcome, after adjustment for confounders, the association with CRTI was stronger for those with more severe injuries.

DISCUSSION

In this baseline analysis of the ADVANCE cohort study, we found that CRTI was associated with an increased prevalence of MetS and greater relative large artery stiffness compared with a frequency-matched group of uninjured military combat veterans exposed to the same operational environment. These associations were stronger with greater injury severity. We also observed greater visceral fat area, systemic inflammation (hs-CRP) and lower recommended physical activity among participants with CRTI, which were exacerbated by worsening injury severity. This suggests that CRTI and worsening injury severity may be associated with increased cardiovascular risk.

MetS and arterial stiffness are of major clinical importance given their strong inter-relationship and independent links to MACE.[6 23] MetS is a complex disorder involving a clustering of cardiovascular risk factors characterised by adipocytokine release, insulin resistance, renin-angiotensin-aldosterone and sympathetic nervous system activation, oxidative stress, low-grade inflammation and endothelial dysfunction.[6] It predisposes to type 2 diabetes, atherosclerosis and increasing arterial stiffness.[8]

In this study the higher prevalence of MetS in the CRTI group was characterised by greater AWC and triglyceride levels and lower HDL-cholesterol, without notable differences in blood pressure or glucose; again these differences were greater with worsening injury severity. In a recent retrospective study (n=772) of injured US military war veterans of similar age and combat experience to ADVANCE, Bhatnagar *et al*[11] reported a higher prevalence of MetS among amputees with CRTI compared with a non-amputee CRTI control group. In their study only three (fasting and non-fasted triglycerides, HDL-cholesterol and blood pressure) out of the five established MetS diagnostic criteria[7] were available. The lower eGDR in our study suggests greater relative insulin resistance with CRTI and worsening injury severity. The greater visceral fat area among the participants

Key messages

What is already known on this subject?

- Recent conflicts in Afghanistan and Iraq have led to the survival of injured servicemen with severe injuries than previously would have been very unlikely without modern improvements in combat-related healthcare.
- The longer-term health consequences of these severe traumatic injuries remain unclear.
- A recent systematic review and meta-analysis of searches on PubMed, Embase, ProQuest and Cumulative Index to Nursing and Allied Health Literature databases and Cochrane reviews from 1 January 1980 to 21 December 2018 identified 26 studies that examined the relationship between combat-related traumatic injury (CRTI) and cardiovascular risk.
- The results indicated that the quality and strength of evidence to support the concept are modest, at best, and derived from retrospective cohort studies (n=12) of injuries sustained ≥40 years ago or of small cross-sectional surveys (n=14) without well-defined control groups.
- There is a need for a contemporary prospective study to examine the cardiovascular effects of CRTI.

What might this study add?

- ADVANCE (ArmeD SerVices TrAuma RehabilitatioN OutComE) is the first prospective cohort study to examine the relationship between contemporary CRTI and long-term health outcomes.
- The cardiovascular risk profiles, with an emphasis on metabolic syndrome and arterial stiffness, of servicemen who had sustained significant CRTI were compared with an uninjured group of servicemen frequency-matched by age, rank, regiment, role-in-theatre and time of deployment.
- Injury severity was independently, and in an 'exposure'-dependent manner, associated with both metabolic syndrome and the arterial augmentation index.

How might this impact on clinical practice?

- This study provides evidence that CRTI and its worsening severity are associated with increased early cardiovascular risk with an increase in both metabolic syndrome and arterial stiffness.
- This has important potential implications for the future health of service personnel and others who sustain severe physical trauma.
- The continued follow-up of this cohort will help determine if these findings translate into clinical events and whether targeted primary prevention strategies to the more severely injured might be indicated.

with CRTI and its worsening severity compounds their cardiovascular risk. Increased visceral fat is an independent predictor of MACE.[24]

cAIx and PWV reflect the cumulative effects of multiple individual cardiovascular risk factors (lipids, glucose, obesity (MetS) and inflammation) acting on the arterial wall, leading to a reduction in arterial compliance and increased arterial stiffness.[23] Hence, cAIx is more than just a cardiovascular risk marker and can be considered an intermediary outcome measure.[23] While PWV and blood pressures were similar, cAIx was significantly higher among the CRTI group and with greater injury severity. As cAIx relates to arterial wave reflection and endothelial function, it may be more vulnerable to earlier changes in arterial haemodynamics and microvascular resistance than PWV.[10 23] This could explain why cAIx was greater yet PWV similar in the CRTI group versus the uninjured group. cAIx is one of the strongest independent predictors of future hypertension in adults with normotension and is known to correlate with established cardiovascular risk factors (eg, age, hs-CRP, lipids, lower physical activity and abdominal obesity), as observed in this study, and MACE.[23] In a recent meta-analysis of 24 prospective cohort studies (n=146 986), a 10% increase in cAIx was associated with a pooled HR of 1.19 (95% CI 1.05 to 1.34) for all-cause mortality and 1.18 (95% CI 1.09 to 1.27) for MACE.[25] We hypothesise that the longitudinal expression of these cardiovascular risk factors in the CRTI group will translate into significantly greater PWV and MACE than that of the uninjured group.

One plausible explanation for the increased burden of MetS and cAIx with CRTI could be their relatively lower physical activity and function (6MWD). Lower physical activity is strongly linked to abdominal obesity, dyslipidaemia, vascular inflammation, insulin resistance, MetS and arterial stiffness.[26] In this study CRTI and greater injury severity were associated with lower weekly physical activity and 6MWD. 6MWD was lower with MetS and inversely correlated with cAIx. Lower physical activity was independently associated with cAIx, but not MetS.

Lower SEC has an inverse relationship with adverse cardiovascular health,[27] an association apparent for both cAIx and MetS, and independent of injury, in this study. The reasons for this association relate to the interaction of societal factors (eg, childhood deprivation, education, income, access to healthcare) and behaviours (eg, diet and smoking) operating from early life, and even in utero, that act to promote cardiovascular risk.[8 27] It is notable that several of the cardiovascular risk factors that were more common in the CRTI group (eg, lower physical activity and HDL-cholesterol and greater triglycerides and abdominal obesity) and linked to lower SEC are modifiable.[27] This observation creates the opportunity to introduce targeted prevention strategies to mitigate this risk.

The observation of higher hs-CRP with CRTI is novel. hs-CRP is a marker of systemic inflammation and a mediator of atherosclerosis.[28] It has been shown that systemic inflammation leads to a decrease in wave reflections and an increase in cAIx, even in healthy adults.[29] In general hs-CRP levels <1.0 mg/L and 1.0–3.0 mg/L are indicative of low and moderate cardiovascular risk, respectively.[28] The relatively higher hs-CRP and heart rates in the CRTI group imply greater systemic inflammation and potentially arterial sheer stress, which is proatherosclerotic.[28]

Limitations

This study has a number of limitations. Our findings are based on a cross-sectional analysis of a cohort at its inception and cannot be used to infer causation. Nonetheless, the prospective nature of ADVANCE, the 'dose'-dependent findings and their biological plausibility are informative in this respect. Based on the distribution of NISS, a value of 13 (the median) was used to categorise injury severity; in a recent US Defense trauma registry of 22 218 patients (injured 2008–2016), this cut-off was the optimal predictor of all-cause mortality and adverse trauma outcomes.[30] While our analyses have identified multiple cardiovascular risk markers to be greater in the injured group, average values were still largely within normal ranges. The continuing follow-up of the ADVANCE cohort will be crucial to the understanding of the impact of CRTI on clinical outcomes. Finally, the influence of other potential cardiovascular risk factors/modifiers, such as

diet, psychosocial factors (eg, post-traumatic stress disorder and depression) and chronic pain, has not been examined here but is the subject of further ADVANCE research.

CONCLUSIONS

This study is the first to investigate the relationship between CRTI, MetS and arterial stiffness. CRTI was independently associated with increased MetS and early markers of arterial stiffness. These risks were more pronounced with worsening injury severity and were independent of age, SEC, physical activity, ethnicity and time from injury. It remains uncertain whether they will translate into MACE over time; this question and the mechanism(s) behind these associations are the subject of ongoing research within the ADVANCE cohort.

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