Injury, Mental illness, Psychological thriving and cardiovascular health amongst CombaT injured and uninjured UK military Servicemen (IMPACTS)

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PhD Dissertation

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INJURY, MENTAL ILLNESS, PSYCHOLOGICAL THRIVING AND CARDIOVASCULAR HEALTH AMONGST COMBAT INJURED AND UNINJURED UK MILITARY SERVICEMEN (IMPACTS) 1

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List of published academic papers incorporated into thesis

Chapter 1, Paper 1: The association between PTSD and cardiovascular disease and its risk factors in male veterans of the Iraq/Afghanistan conflicts: a systematic review

Dyball, D., Evans, S., Boos, C. J., Stevelink, S. A.M., & 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. *International Review of Psychiatry*, *31*(1), 34-48.
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Chapter 2, Paper 2: (Joint first author) 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

Bennett, A. N., Dyball, D. M., Boos, C. J., Fear, N. T., Schofield, S., Bull, A. M., & 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.
http://dx.doi.org/10.1136/bmjopen-2020-037850

Chapter 3, Paper 3: 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

Dyball, D., Bennett, A. N., Schofield, S., Cullinan, P., Boos, C. J., Bull, A. M., ... & 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. *The Lancet Psychiatry*, *9*(7), 547-554. https://doi.org/10.1016/S2215-0366(22)00112-2

Chapter 4, Paper 4: Post-Traumatic Growth amongst UK Armed Forces personnel who deployed to Afghanistan and the role of combat injury, mental health and pain: The ADVANCE cohort study

Dyball, D., Bennett, A. N., Schofield, S., Cullinan, P., Boos, C. J., Bull, A. M., ... & Fear, N. (2022). Post-Traumatic Growth amongst UK Armed Forces personnel who deployed to Afghanistan and the role of combat injury, mental health and pain: The ADVANCE cohort study. *Psychological Medicine*. https://doi.org/10.1017/S0033291722002410

Chapter 5, Paper 5: The underlying mechanisms by which PTSD symptoms are associated with cardiovascular heath in male UK military personnel: The ADVANCE cohort study

Dyball, D., Bennett, A. N., Schofield, S., Cullinan, P., Boos, C., Bull, A. J., ... & Fear, N. T. (2023). The underlying mechanisms by which PTSD symptoms are associated with cardiovascular heath in male UK military personnel: The ADVANCE cohort study. *Journal of Psychiatric Research*. https://doi.org/10.1016/j.jpsychires.2023.01.010

List of academic papers submitted for publication incorporated into thesis, not currently accepted

Chapter 6, Paper 6: The underlying mechanisms by which Post-Traumatic Growth is associated with cardiovascular health in male UK military personnel: The ADVANCE cohort study

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List of relevant published academic papers not incorporated into thesis, published during PhD (including co-authorship)

Paper 1: Do serving and ex-serving personnel of the UK armed forces seek help for perceived stress, emotional or mental health problems?

Stevelink, S. A., Jones, N., Jones, M., Dyball, D., Khera, C. K., Pernet, D., ... & Fear, N. T. (2019). Do serving and ex-serving personnel of the UK armed forces seek help for perceived stress, emotional or mental health problems?. *European journal of psychotraumatology*, *10*(1), 1556552. DOI: 10.1080/20008198.2018.1556552

Paper 2: The relationship between military combat and cardiovascular risk: a systematic review and meta-analysis

Boos, C. J., De Villiers, N., Dyball, D., McConnell, A., & Bennett, A. N. (2019). The relationship between military combat and cardiovascular risk: a systematic review and meta-analysis. *International journal of vascular medicine*, *2019*. DOI: 10.1155/2019/9849465

Paper 3: Association between combat-related traumatic injury and cardiovascular risk

Boos, C. J., Schofield, S., Cullinan, P., Dyball, D., Fear, N. T., Bull, A. M., ... & Bennett, A. N. (2022). Association between combat-related traumatic injury and cardiovascular risk. *Heart*, *108*(5), 367-374. DOI: 10.1136/heartjnl-2021-320296

Paper 4: Post-Traumatic Growth amongst UK Military Personnel Deployed to Iraq or Afghanistan: data from phase 3 of a military cohort study

Dyball, D., Taylor-Beirne, S., Greenberg, N., Stevelink, S., & Fear, N. (2022). Post-traumatic growth amongst UK military personnel deployed to Iraq or Afghanistan: Data from phase 3 of a military cohort study. *British Journal of Psychiatry Open*. DOI: 10.1192/bjo.2022.570

Abstract

Introduction: Emergency medicine has developed to the point that military personnel in recent conflicts (e.g. Afghanistan) are surviving physical combat injuries that would have previously resulted in mortality. The long-term health implications of such injuries are largely unknown.

Aims: This thesis sets out to describe the rates of mental illness (Post-Traumatic Stress Disorder (PTSD), depression, anxiety and mental health multimorbidity) and psychological thriving (Post-Traumatic Growth (PTG)) amongst a cohort of physically injured UK military personnel and an uninjured comparison group. This thesis also explores the psychological and biological mechanisms by which PTSD and PTG are associated with cardiovascular health/cardiovascular disease risk factors.

Methods: 1145 UK military personnel completed a comprehensive health assessment as part of the ADVANCE cohort study at Defence Medical Rehabilitation Centre Headley Court (2015-2018) or Stanford Hall (2018-2020). 579 participants sustained a physical combat injury whilst on deployment to Afghanistan, and 566 were a frequency-matched uninjured comparison group based on age, rank, deployment role, regiment and deployment era. Health assessments included venous blood sampling, Vicorder assessment, dual-energy absorptiometry and validated self-report mental health questionnaires.

Statistical techniques: Logistic regression modelling, multinomial logistic regression, generalised structural equation modelling, bootstrapping and variable selection procedures including bootstrapped inclusion frequencies and model averaging.

Results: Physically combat injured personnel were more likely to report probable depression, anxiety, PTSD, mental health multimorbidity and PTG compared to the uninjured group. Heterogeneity between estimates was observed depending on subtypes of injury. Personnel with an amputation injury reported similar rates of mental illness compared to the uninjured group, and those with non-amputation injuries reported higher rates. Inversely, personnel with amputation injuries reported more PTG compared to the uninjured group, whereas those with non-amputation injuries reported similar rates of PTG. Associations between combat injury and PTG were partially mediated by depression, PTSD and current moderate-extreme pain.

Investigation of PTSD symptom clusters (avoidance behaviours; emotional numbing; hyperarousal and intrusive thoughts) and cardiovascular disease risk factors found that a diverse combination of symptom clusters were associated with cardiometabolic effects (insulin resistance, visceral fat, lipids) and haemodynamic functioning (resting heart rate and systolic blood pressure), but not inflammation (high sensitivity C-reactive protein). Associations between PTG factors (appreciation of life; new possibilities; personal strength; relating to others and spiritual change) found that these were associated with mostly positive (diastolic blood pressure and lipids), but also negative (fasting blood glucose and lipids) cardiometabolic effects and haemodynamic functioning. PTG factors were not associated with inflammation (high sensitivity C-reactive protein).

Discussion: The journey to recovery for UK military personnel who survived a physical combat injury does not end after discharge from Defence Medical Rehabilitation Centre services. Those who sustained non-amputation injuries are at higher risk for probable mental illness, whilst those who sustained amputation injuries are more likely to experience PTG compared to those who deployed to Afghanistan and were uninjured. This may be due to social factors such as hierarchy of wounding or increased and easier access to therapeutic or charitable support services for those with amputation injuries, though more research is required to understand if this is true. This thesis presents evidence that PTSD symptoms are associated with increased cardiovascular risk and PTG is associated with mostly reductions in cardiovascular risk several years after exposure to warzones/injury. Whether the association between psychological symptoms and cardiovascular risk translates to later development of cardiovascular disease remains to be seen. Results from this thesis suggest that a focus on policy/intervention that facilitates both physical and psychological thriving would be beneficial for the long-term health of UK military personnel, especially if they sustained a physical combat injury.

Declaration

This thesis consists of work on the ADVANCE cohort study, a collaboration between King's College London, Imperial College London and the UK Ministry of Defence. I (Daniel Dyball) was not involved in the design or ethics of the ADVANCE study. I have worked part-time (0.8 FTE) as a research assistant for the ADVANCE cohort study since 2017, and have been involved in recruitment, data collection, data cleaning and ethics amendments since this point.

Additional data collected for my study, herein described as the IMPACTS study, started after an ethics amendment in 2018 and participants were automatically enrolled if they visited the ADVANCE cohort study after the amendment. Participants who visited before this date were offered to complete the additional IMPACTS questionnaires via post/online, and I was responsible for recruitment of these participants. Please see chapter two pg. 130 for more details.

The aims and hypotheses of this thesis were developed by myself, with input from my supervisors. The statistical approach was also developed by myself, with input from my supervisors and the ADVANCE cohort study statistician, Susie Schofield.

This thesis and all publications herein were supervised by Professor Nicola T Fear, Dr Sharon Stevelink and Gp Capt Alex Bennett.

Statement of authorship

I (Daniel Dyball) carried out all drafting, analysis and write up of this thesis. Professor Nicola Fear, Dr Sharon Stevelink and Gp Capt Alex Bennett provided feedback on the thesis and all incorporated submitted and accepted publications. Susie Schofield provided statistical advice on all incorporated submitted and accepted publications. All other co-authors provided feedback on all incorporated submitted and accepted publications. I was the first author in all publications incorporated in this thesis with exception to the ADVANCE cohort protocol paper (chapter two, pg. 106-130), where I was joint first author.

COVID-19 Impact Statement

COVID-19 put a halt to all recruitment to the ADVANCE cohort study between March 2020 and August 2020 and no data collection took place during this time. Restrictions on work took place during the lockdown periods between 2020 and 2021. Sample size for the cohort was affected by these delays.

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I would like to thank each of my supervisors for their unique impact on my work during my PhD. Dr Sharon Stevelink, thank you for your great attention to detail. I hypothesise that the number of comments you provided would be positively correlated with the overall quality of my work ($p<.01$). Gp Capt Alex Bennett, thank you for your clinical expertise and continual supply of prosecco during the holidays. I am positive I will hear your sigh of relief upon me submitting my thesis all the way from London. Professor Nicola Fear, thank you for being a guiding force during my PhD and stopping me from going down too many 'rabbit holes' of theories, statistical approaches, or entirely separate research questions. I would also like to thank Susie Schofield for entertaining the few rabbit holes of hyper-fixation I did manage to sneak past professor Fear. Our debates led to what I think is a strong statistical foundation from which my work has been set.

The wider team on the ADVANCE study require additional acknowledgement, as without their work and support none of this would have been possible. The clinical team, administrative team and project board, spread across both different universities and locations, have all been wonderful. Specific mention must be made of Melanie Chesnokov and Sarah Evans, whose continued positive outlook juxtaposed my sarcasm and nihilism perfectly.

Finally, I would like to thank my grandparents David and Marlene Lacey. They have waited patiently for me to finally become a doctor, even if they probably still do not quite understand what it is that I do. Though frankly, I suspect not even my closest friends truly understand what I am on about most of the time either.

Abbreviations

Abbreviation	Meaning
ADVANCE	ArmeD SerVices TrAuma and RehabilitatioN OutComE study
AHSC	Academic Health Science Centres
AOL	Appreciation Of Life
AOR	Adjusted Odds Ratio
BPM	Beats Per Minute
CI	Confidence Interval
CMD	Common Mental Disorders
DBP	Diastolic Blood Pressure
DEXA	Dual Energy X-ray Absorptiometry
DMRC	Defence Medical Rehabilitation Centre
DPTGI	Deployment-related Post-Traumatic Growth Inventory
DSM	Diagnostic Statistical Manual
GAD	Generalised Anxiety Disorder
GSEM	Generalised Structural Equation Modelling
HDL	High-Density Lipoproteins
HIV	Human Immunodeficiency Virus
HsCRP	High sensitivity C-Reactive Protein
ICD	International Classification of Disease
IED	Improvised Explosive Device
IMPACTS	Injury, Mental illness, Psychological thriving and cArdiovascular health amongst CombaT injured and uninjured UK military Servicemen
IQR	Interquartile Range
ISS	Injury Severity Score

Abbreviation	Meaning
LDL	Low-Density Lipoproteins
NCO	Non-Commissioned Officer
NHS	National Health Service
NISS	New Injury Severity Score
NP	New Possibilities
OR	Odds Ratio
PCL	Post-traumatic stress disorder Check List
PHQ	Patient Health Questionnaire
PS	Personal Strength
PTG	Post-Traumatic Growth
PTGI	Post-Traumatic Growth Inventory
PTSD	Post-Traumatic Stress Disorder
PWV	Pulse Wave Velocity
RCDM	Royal Centre for Defence Medicine
RPG	Rock Propelled Grenade
RRR	Relative Risk Ratio
RTO	Relating To Others
SBP	Systolic Blood Pressure
SC	Spiritual Change
SEM	Structural Equation Modelling
SNCO	Senior Non-Commissioned Officer
SSAFA	Soldiers, Sailors, Airmen and Families Association
TILS	Transition, Intervention and Liaison Service
UK	United Kingdom

Abbreviation	**Meaning**
US	United States
VAT	Visceral Adipose Tissue

Glossary of terms

Word	Meaning
Amputation	Refers to the whole or partial removal of limbs. For a full break down of major limb amputation types, please see Chapter 1 Figure 2.
Armed Forces	Military personnel who served in the Royal Navy, Royal Marines, Army or Royal Air Force.
Artery	Tubes forming part of the circulatory system carry blood away from the heart.
Blood pressure	Overall resistance to the blood flow (pressure) in your arteries.
Cardiovascular	Relating to the heart and vascular (blood vessel) system.
Cholesterol	Lipids created to transfer energy to cell through the circulatory system to aid in cell repair.
Closed fracture	Fracture of the bone without associated soft tissue damage.
Combat role	Personnel who served in direct combat roles, e.g. Royal Infantry.
Combat Service Support	Personnel who served in logistical/medical roles, e.g. Medics.
Combat Support	Personnel who served in engineering/telecommunications/artillery roles e.g. Royal Engineers.
Cortisol	Otherwise known as the ‘stress hormone’, cortisol is a glucocorticoid hormone that

Word	Meaning
	increases glucose in the blood steam.
Diastolic blood pressure	Pressure in your arteries in-between heart beats.
Dual Energy X-ray Absorptiometry	A spectral imaging device used for the assessment of body fat and bone mineral density.
Dyslipidaemia	Lipid levels outside the normal clinical range. Includes hyperlipidaemia, e.g. above the normal clinical range of lipids.
Endothelial	Refers to the single layer of cells along the vessel walls in arteries/veins.
Engagement status	Regular (full time) serving or reservist roles.
Ex-serving personnel	Personnel who have left military service, also known as 'Veterans'.
Fasting Blood Glucose	Glycated haemoglobin level after fasting.
Fragmentation injury	Injuries sustained from highly energised fragments, usually from blasts or IEDs.
HBA1c	Glycated haemoglobin level.
Heart Rate Variability	A global term used to account for the time variance between beats of the heart.
High Sensitivity C-Reactive Protein	A type of Messenger RiboNucleic Acid (M-RNA) involved in the inflammation process.
High-Density Lipoprotein	Otherwise known as 'good cholesterol', is a lipid which transfers cholesterol from the body back to the liver.
Hypertension	Clinically determined persistent high blood pressure.

Word	**Meaning**
Hypo-Pituitary Adrenal Axis	Relating to processes between the hypothalamus, pituitary gland and adrenal gland.
Inflammation	A term for the global processes involved in the immune system. Includes both the recognition of harmful substances (e.g. bacteria) and removal of these substances from the body.
Insulin	Anabolic hormone produced in the body with a primary function to transfer glucose.
Insulin resistance	Increased insulin resistance refers to an inability for the body to properly absorb insulin.
Lipoprotein	Particles made of protein and fat (lipids).
Low-Density Lipoprotein	Otherwise known as 'bad cholesterol', is a lipid which transfers energy to cells through the circulatory system. Can build up in the circulatory system.
Mental health	Refers to the full spectrum of mental well-being and encompasses both mental illness and psychological thriving.
Mental illness	Psychological disorders that impact on a person's health, behaviours and well-being in a negative way.
Morbidity	Rate of disease.
Mortality	Rate of death.
Negative affect	The experience of negative emotions (e.g. sadness, distress, fear etc.)

Word	**Meaning**
Open fracture	Fracture of the bone with associated soft tissue damage.
Operation BANNER	UK operational title for major military deployment to Northern Ireland between 1969-2007.
Operation HERRICK	UK operational title for major military deployment to Afghanistan between 2002-2014.
Operation FINGAL	UK operational title for major military deployment to Afghanistan between 2001-2002.
Operation TELIC	UK operational title for major military deployment to Iraq between 2003-2011.
Optimism	Relating to a sustained positive outlook of the future.
Positive affect	The experience of positive emotions (e.g. happiness, enthusiasm, joy etc.)
Post-Traumatic Growth	Beneficial psychological change that occurs after experiencing a traumatic event.
Post-Traumatic Stress Disorder	A mental illness occurring after direct/indirect exposure to a trauma, defined by a cluster of symptoms that include intrusive, avoidance, negative alterations in cognitions or mood and possible alterations in arousal or reactivity. Symptoms must last for greater than one month and must not be due to drug use or other illness.
Psychological thriving	Positive psychological functioning. Can include aspects such as gratitude, optimism,

Word	Meaning
	post-traumatic growth, and more.
Pulse Wave Analysis	Estimation of cardiac output based on continuous analysis of arterial blood pressure.
Pulse Wave Velocity	A measurement of arterial stiffness, estimating the velocity at which blood pressure circulates from the circulatory system over distance travelled.
Shrapnel	The material dispersed from anti-personnel weaponry (e.g. grenade, IED etc.).
Systolic blood pressure	Pressure in your arteries during heart beats.
Triglycerides	Lipids created from unused calories from food, stored in fat tissue.
Vascular	Also known as the circulatory system, refers to the vessels that supply blood throughout the body.
Vein	Tubes forming part of the circulatory system carrying blood towards the heart.
Veteran	Ex-serving personnel. In US literature, may refer to military serving personnel who have deployed and returned to a specific deployment, e.g. a veteran of Afghanistan.
Vicorder	A clinical machine used for non-invasive vascular testing.
Visceral Adipose Tissue	Hormonally active component of total body fat.
Whole Blood	A measure of blood including all of its components (e.g. red blood cells, white

Word	**Meaning**
	blood cells, platelets and plasma).
Wound debridement	Removal of foreign objects and cleaning of injured tissue.

Thesis Structure

Chapter one (pg. 25-81) describes the literature available relating to combat injuries and mental health of the UK Armed Forces who deployed to Iraq/Afghanistan, including mental illness, e.g. depression, anxiety and Post-Traumatic Stress Disorder (PTSD) and psychological thriving, e.g. Post-Traumatic Growth (PTG). The chapter also includes details of the biological pathways between mental health and cardiovascular disease (pg. 47-81), as well as a systematic review of the link between PTSD and cardiovascular risk in military personnel who deployed to Iraq/Afghanistan (pg. 51-78).

Chapter two (pg. 106-151) describes the methodologies used throughout my thesis, including the protocol paper of the ADVANCE cohort study (pg. 106-130), which provided the foundation from which this thesis was set.

Chapters three to six describe the results of the thesis, including the mental health outcomes of male UK military personnel deployed to Afghanistan and the role of combat injury (chapter three, pg. 167-187); PTG amongst UK Armed Forces personnel who deployed to Afghanistan and the role of combat injury, mental health and pain (chapter four, pg. 193-217); The underlying mechanisms by which PTSD symptoms are associated with cardiovascular heath in male UK military personnel (chapter five, pg. 223-252); and The underlying mechanisms by which PTG is associated with cardiovascular health in male UK military personnel (chapter six, pg. 257-287).

Chapter seven (pg. 295-320) presents additional discussion of the thesis, including strengths, weaknesses and clinical/policy implications.

Introduction

"What are the known physical and mental health consequences of combat injury?"

Overview

In this chapter, I discuss the UK Armed Forces' military deployment to Afghanistan between 2002-2014, with a focus on the mechanisms of combat injuries sustained by UK military personnel as well as the observed health-related sequalae of these types of injuries. Physical injury profiles are categorised by amputation and non-amputation injuries. Mental health consequences are also described and explored, including both mental illness (common mental disorders, post-traumatic stress disorder and mental health multimorbidity) and psychological thriving (post-traumatic growth). Finally, the theoretical mechanisms by which mental health, encompassing both mental illness and psychological thriving, affect the cardiovascular system are explained.

UK Armed Forces in Afghanistan

The UK Armed Forces deployed to Afghanistan between 2001 and 2014. Operation FINGAL occurred between 2001-2002 and was followed by Operation HERRICK, which occurred between 2002-2014. Over 140000 UK Armed Forces personnel deployed to Operation HERRICK (1). Between 2001 and 2020, 457 UK Armed Forces personnel died in operations in Afghanistan[1]. The peak number of deaths occurred in 2009 and 2010, with over 100 deaths reported in each year (2). In these years UK Armed Forces personnel also experienced a peak in the number of severe physical combat injuries from Afghanistan, with over 150 personnel experiencing a very serious injury/serious injury[2] in 2009/2010 and 616 personnel experiencing a very serious injury/serious injury over the whole deployment period (2, 3).

The use of improvised explosive devices has increased over the past half century, with the UK Armed Forces being increasingly exposed to these devices during deployments with asymmetric warfare (e.g. the war on terror, guerrilla warfare) (4). With this increased exposure comes increased risk of severe injury profiles mostly focussed on the extremities, often including amputation injuries, but also abdominal, genital and proximal injuries (5).

Deployments to Afghanistan in particular represent a unique time in medical and research history. Due to advances in medical science and defence technology, many military personnel, who would have died due to the severity of their injury in any previous engagement, survived. Compared to previous deployments to Operation BANNER (the term used for operations in Northern Ireland between 1969 and 2007) and Operation TELIC (the term used for operations in Iraq from 2003-2009), increased probability of survival for Operation HERRICK was noted for those injured by an IED explosion at higher levels of injury severity (4, 6). Using the New Injury Severity Score (NISS), a measurement of anatomical injury using the three most severely injured body regions (7), it was found that a 50% survival rate was associated with a NISS score of 29 for Operation BANNER, which significantly (statistics not reported) rose to 43 for Operation HERRICK, indicating a greater chance of survival for more severely injured personnel (4). Similarly, a separate analysis of

[1] Numbers from this report include the most up to date details regarding Operation HERRICK, but also include numbers from operations in Afghanistan that were not part of Operation HERRICK.

[2] Very seriously injured indicates that the injury was so severe that there is imminent risk of mortality. Seriously injured indicates that the injury, whilst of concern, does not have an associated imminent risk of mortality.

UK military personnel with thoracic injuries from Iraq or Afghanistan between 2003-2008 and 2009-2011 found that the percentage of unexpected survivors, based on a combined injury severity score (TRauma Injury Severity Score (TRISS)) of <50%, increased from 3.5% to 9.4% (p=0.01) (8).

Surviving increasingly severe injuries may result in considerable reductions in quality of life, increased disability and requires substantial rehabilitation and quality care (9-11). The Defence Medical Rehabilitation Centre (DMRC), originally located at Headley Court and now located at Stanford Hall, provided this initial care to injured UK Armed Forces personnel alongside the Royal Centre for Defence Medicine (RCDM) in Birmingham. Between 2009 and 2010 during operation HERRICK, the timeframe in which operational intensity was at its highest, RCDM and DMRC had 208 patients requiring a high level of medical and rehabilitation care (12). At DMRC, an interdisciplinary team of doctors, physiotherapists, mental health practitioners, social workers, key-workers and prosthetics engineers worked together to help injured personnel attempt to attain the highest level of functioning possible. After rehabilitation, generally these injured military personnel were medically discharged and their care was transferred to the UK National Health Service (NHS). Additional care was and continues to be available from the charitable sector.

Little is known about the long-term health impact of sustaining a combat injury following discharge from DMRC. The UK Government Strategy for our Veterans has identified that whilst more veterans have survived more severe injuries than at any other time point, the physical and mental health needs of this group are unknown and work is required to understand their specific needs, particularly as this group ages and these needs evolve/change (13).

Pages 28-47 of this thesis shall explore the mechanisms and types of injuries that were experienced during deployments to Operation HERRICK and the known sequalae of such injuries.

Physical injuries and consequences

Mechanism of injuries

Due to the cross over in time, the reasons for invasion and close geographical location, figures and investigations of the UK military involvement in Afghanistan (Operation HERRICK) are often combined with UK military operations conducted in Iraq (Operation TELIC). It is of note however that significant differences in injury profiles have been

recognised between the operations[3]. A greater proportion of UK Armed Forces personnel sustained fatal neck and spine injuries during Operation TELIC and a greater proportion of fatal abdomen, upper extremity and lower extremity injuries were sustained during Operation HERRICK (4). A greater proportion of personnel with abdomen, spine, lower extremity injuries survived during Operation HERRICK compared to Operation TELIC. Differences in injury/survival profiles between operation TELIC and operation HERRICK may be explained by differences in methods used to deploy IEDs against dismounted personnel, differences in level of protection offered to the thoracoabdominal region by body armour, and higher rates of injuries sustained in vehicles during operation TELIC compared to operation HERRICK (4).

Figures available on the mechanisms of injuries from deployments to Iraq/Afghanistan report that injuries resulting from explosions were most prevalent, comprising of approximately 56% of total injuries for UK military personnel (10) (Chapter 1 Table 1) and 72% of all injuries among NATO countries in the Iraq/Afghanistan conflicts (14). Gunshot injuries were the second most common type of injury after explosive injuries in the UK military during those deployments (6), comprising of approximately 24% of total injuries for UK military personnel (10) (Chapter 1 Table 1) and 18% of all injuries among NATO countries in the Iraq/Afghanistan conflicts (14).

Injuries from explosions were experienced by over 5000 UK military personnel, with a mean NISS of 9 (4). 65% of casualties from hostile actions in Iraq/Afghanistan between 2003-2012 were caused by explosive weapons (6). Gunshot wounds which did not result in death were experienced by 546 UK military personnel from deployments to Iraq/Afghanistan between 2003-2014 (10). 31% of casualties from hostile actions in Iraq/Afghanistan between 2003-2012 were caused by gunshot (6). It is of note that gunshot wounds may not carry a particularly high injury severity score (15). The majority of explosive and gunshot wound injuries were located in the extremities, which is likely a reflection of significant improvements in body armour over the last 80 years (6, 16, 17).

[3] *Where possible, this thesis will focus on details from Afghanistan, specifically Operation HERRICK.*

CHAPTER 1 TABLE 1: MECHANISM OF INJURY FOR UK MILITARY PERSONNEL IN IRAQ/AFGHANISTAN CONFLICTS (ADAPTED FROM STEVENSON ET AL., 2018; (10))

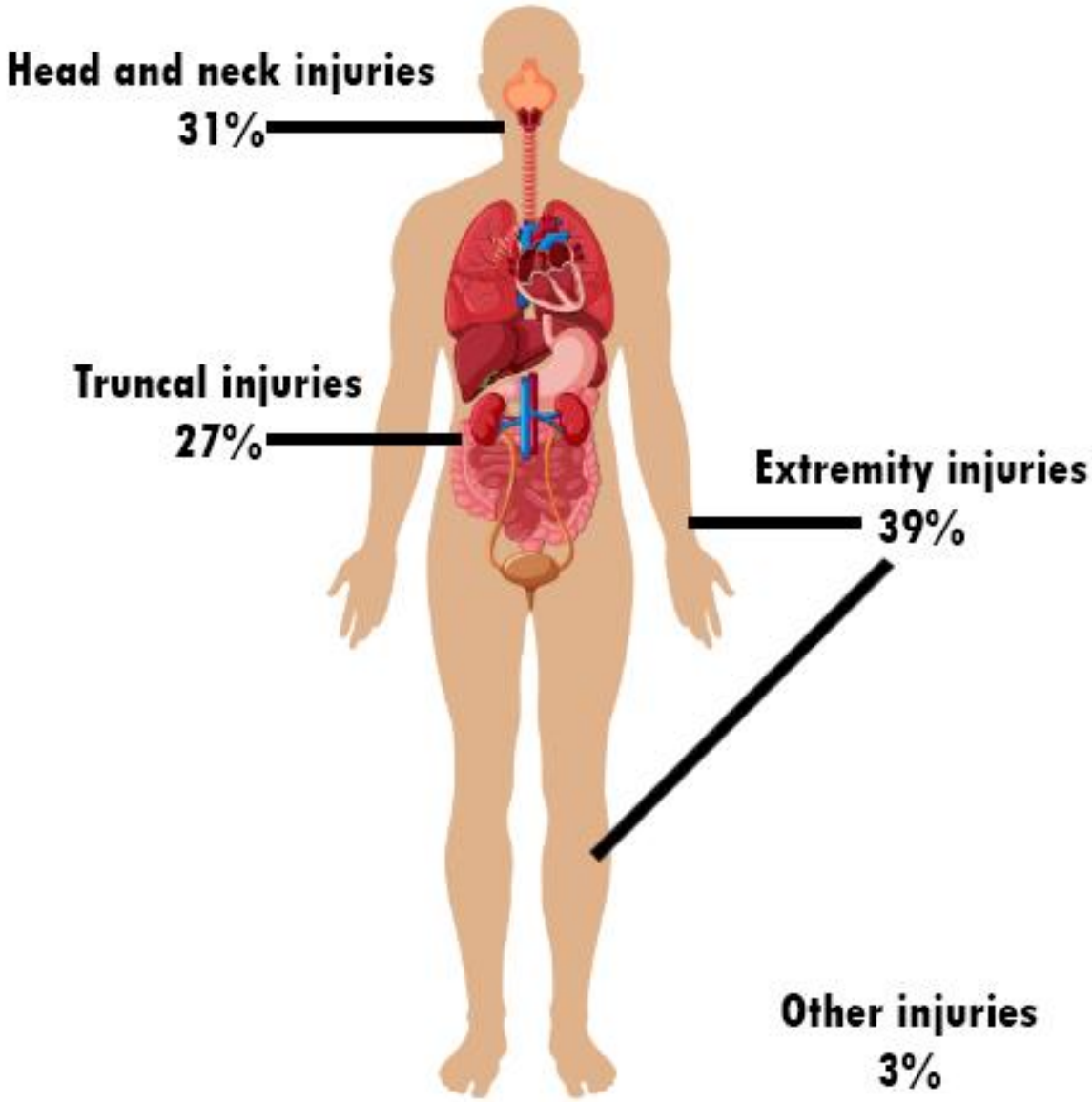
Mechanism of Injury	***n (%)***
Explosive	**1694 (56.7)**
Gunshot wound	**723 (24.2)**
Motor Vehicle Collision	**163 (5.5)**
Fall	**111 (3.7)**
Other	**93 (3.1)**
Crush	**71 (2.4)**
Aircraft Incident	**67 (2.2)**
Burn	**43 (1.4)**
Assault	**21 (0.7)**
Total	**2986 (100.0)**

The nature of explosive events can lead to blunt force trauma, shockwave, burn and crushing injuries depending on the primary, secondary, tertiary, quaternary or quinary blast injury mechanism. Primary blast injury refers to injuries sustained from the waveform of the blast, which affects structures such as the lungs, gastrointestinal tract or other gas filled structures (18). Secondary blast injuries refer to injuries from highly energised projectiles, similar to gunshot wounds (19). These high energy projectiles cause damage to the tissue through the force they exert such as breaking, crushing or burning soft tissue through dissipation of thermal and kinetic energy. These projectiles also potentially contaminate the individual with foreign materials such as bullet fragments or shrapnel (20). Tertiary blast injury refers to acceleration of the body itself due to the energy transmitted from the explosion, often resulting in blunt force trauma but can also cause penetrating or fracture injuries (18). Quaternary blast injuries refer to injuries sustained due to exposure to products of the explosion, for example heat, light, or gases. Quinary blast injuries refer to injuries/illnesses sustained as a result of exposure to post-explosion environmental contaminants, e.g. bacteria. It is noteworthy that blast characteristics (e.g. primary/secondary) are not regularly available

in the medical records of Armed Forces personnel and as a result are not regularly reflected in the literature (18).

Location of injuries sustained from blasts or other mechanisms of injury are important to consider as they can have substantial consequences on mortality risk, risk of disability and lower quality of life (21-23). The anatomical distribution of combat injuries sustained in the Iraq/Afghanistan conflicts by NATO coalition forces can be found in Chapter 1 Figure 1.

CHAPTER 1 FIGURE 1: ANATOMICAL DISTRIBUTION OF WOUNDS BY NATO COALITION FORCES IN IRAQ AND AFGHANISTAN, DATA DERIVED FROM HOENCAMP ET. AL. 2014 (14)



Injury profiles[4]

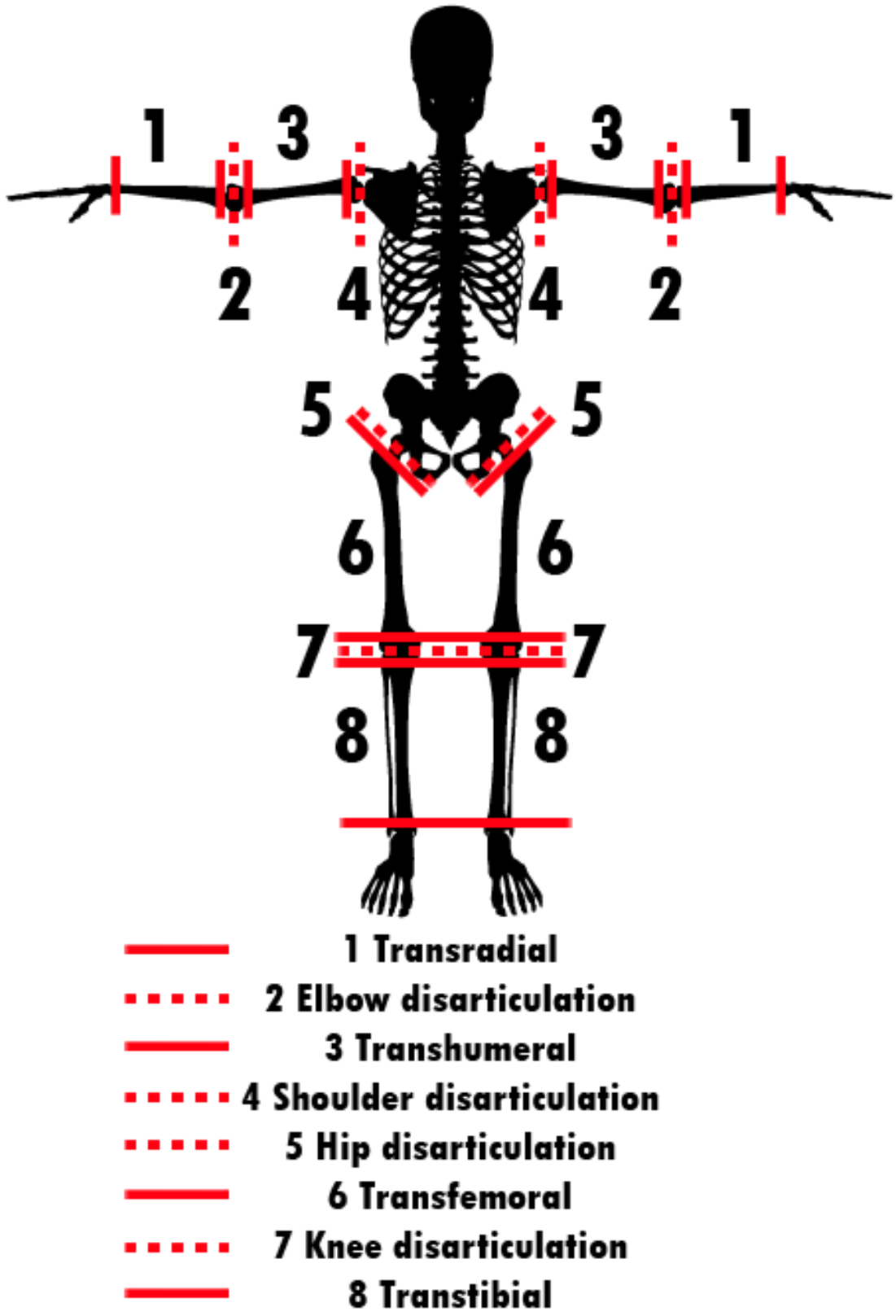
In this thesis, injured groups will be broken down into amputation and non-amputation injuries. Amputation injuries will refer to major limb amputation including shoulder disarticulation and above/through/below elbow arm amputations, as well as hip disarticulation and above/through/below knee leg amputations (Chapter 1 Figure 2). Partial amputations refer to amputations of smaller regions of the body, such as amputations of digits/toes, partial hand or partial foot[5]. Non-amputation injuries simply infer no presence of major limb amputation, and can include any other type of injury (e.g. fragmentation injury, shrapnel injury, fractures). Those who sustained amputation injuries may sustain other types of non-amputation injuries (e.g. genitourinary) as well as their primary amputation injuries.

Sequalae of injury, aspects of health that are affected by the injury, are explored based on the specific types of injuries sustained. There are however sequalae of injury that are generic and might apply to multiple types of injury. For example, those exposed to blast injuries or explosions, regardless of whether they sustained amputation or non-amputation injuries, might have subsequent hearing loss (24).

[4] *Some data on injuries sustained whilst on deployment are suppressed to allow for medical confidentiality of the survivor in line with Defence Statistics rounding policy (https://www.gov.uk/government/publications/defence-statistics-policies/ministry-of-defence-disclosure-control-and-rounding-policy). As such, some data reported in this thesis may be lower than the actual estimates.*

[5] *Partial amputations are defined separately from major amputation injury. In this thesis, an individual who experienced an isolated partial amputation injury without major amputation would form part of the non-amputation injury group. Other papers in the literature may not have made this distinction.*

CHAPTER 1 FIGURE 2: AMPUTATION LABELS BY LOCATION



Amputation injuries

Amputation injuries were often sustained as a result of close proximity to blasts in the Afghanistan conflict, where highly energised fragments from Rocket Propelled Grenades (RPGs) or Improvised Explosive Devices (IEDs) would cause extensive soft tissue damage and complicated fractures (e.g. commuted fractures, denoting fractures where the bone is splintered or crushed, or non-union fractures, denoting fractures which fail to heal), often resulting in wounds at high risk of contamination/infection (25). Previously, early primary amputation, i.e. amputation surgery being completed in the immediate aftermath of injury, was the preferred surgical choice due to it being associated with lower mortality. However, advances in medical science during the Iraq/Afghanistan conflicts meant that limb salvage was an increasingly viable option, and initially minimal differences in outcomes between those who sustained early primary amputation and limb salvage were observed in the literature (26-28).

In an analysis of US military personnel who sustained an amputation injury as a result of IEDs between 2001 and 2011, it was estimated that 87.8 soldiers sustained a major amputation per 100,000 soldier-years (18). Amputation injuries (partial and/or limb) were sustained by 275 UK military personnel whilst deployed to Operation HERRICK, with the peak number of amputations occurring during 2009 (*n*=71) and 2010 (*n*=75) (29). These injured personnel experienced a combined total of 416 amputations, indicating an average of 1.57 limbs amputated per injured personnel. Approximately 140 injured personnel sustained a single amputation between 2006-2014, 101 injured personnel sustained a double amputation and 24 sustained a triple amputation (30). The majority of these amputations would be considered acute amputations (e.g. early primary amputation). However, it is estimated that around 15% of those who sustained an amputation injury had delayed amputations e.g. initial limb salvage attempts took place and actual amputation occurred >3 months after the index injury (31). This is likely due to factors such as persistent limb pain, deep infection or non-union fracture (32). The relative risk of amputation was higher for those who sustained penetrating lower extremity arterial injuries with a blast-mechanism versus a gunshot mechanism (primary amputation RRR 7.88, 95% CI not reported; secondary amputation RRR 2.01 95%CI not reported) (33).

The most common types of amputation injury (partial and/or limb) sustained from Iraq/Afghanistan were lower limb transfemoral or transtibial (30). Upper limb amputations were less common, and mostly transhumeral (34). Combinations of upper limb and lower

limb amputations were prevalent amongst a small number of those injured and were mostly bilateral lower limb combined with unilateral upper limb.

Sequalae of amputation injury

Sustaining an amputation injury can have a considerable impact on your quality of life, physical well-being, mental well-being and functioning (35, 36). Rehabilitation will usually include the fitting of a prosthetic limb to replace the missing limb/s and training in the use of this artificial limb. Despite this, the person with an amputation will have a substantial reduction in functional mobility which will vary significantly depending on the type of amputation they have sustained (e.g. those who sustain below knee amputations or through knee amputations have greater mobility as measured by their ability to walk 500m compared to those who sustain above knee amputations, $p<.01$) (36). It has been observed amongst UK military personnel with unilateral lower limb amputations that those who experienced transfemoral amputations reported significantly greater scores (indicating better health) compared to both those who experienced knee disarticulations ($p<.01$) and transtibial amputations ($p<.001$) on the physical component scores of the SF-36 health survey (including items on physical functioning, physical well-being, bodily pain and general health perception) (37). Scores on the mental health component of the SF-36 (including items on vitality, social functioning, emotional well-being and mental health) did not significantly differ between groups.

Physical health complications due to amputations can be extensive. Infections (e.g. cellulitis, osteomyelitis, septicaemia) complications of the cardiovascular system (e.g. deep vein thrombosis, pulmonary embolisms) and chronic inflammation or inflammatory disorders have been observed in those who have sustained limb amputations (38). Long-term use of prosthetics has been linked to musculoskeletal overuse injuries, with between 59% and 68% of US military personnel with lower limb amputations experiencing these disorders in the lower limb, upper limb or lumbar regions a year post-injury (39). Other issues can include increased rates of osteoarthritis, osteopenia and osteoporosis, back pain, residual limb pain and phantom pain (40). Reduced physical capacity may result in reduced muscle strength, balance and walking ability (e.g. walking symmetry) which in turn may reduce engagement in physical activity (41). Evidence also exists for males sustaining amputation injuries engaging in poor dietary habits and having increased rates of obesity (42).

Sustaining an amputation injury also has a significant impact on one's mental health. In a systematic review on the rates of depression and anxiety following traumatic limb

amputation, rates of depression varied from 20-63% and rates of anxiety varied from 25-57% (43). Similarly in a review investigating the prevalence of mental illness in serving/ex-serving military personnel with a physical impairment, those who sustained an amputation reported rates of depression ranging from 10-32%, rates of anxiety ranging from 16-35% and rates of PTSD ranging from 2-59% (44). Short-term data available for UK military personnel who sustained an amputation found that there were no significant differences in mental health outcomes between those who sustained unilateral, bilateral or triple amputations (45). Timepoint of follow-up varies extensively in the available literature, so it is uncertain what the long-term mental health outcomes might be in this population. In the US, the majority of presentations for mental illnesses from those who sustained amputation injuries whilst on deployment to Iraq/Afghanistan occurred in the first six months post-injury (46). Those who sustained an amputation injury were followed up for two years and it was observed that 83% of patients attended psychiatric therapy in the <2 year period post-injury, with an average (mean) of 21 sessions.

3-18 months post injury, US military personnel who sustained a traumatic amputation injury reported clinically significant pain, 61% reporting residual limb pain and 58% reporting phantom pain (47). In the four years post-injury, a retrospective analysis of medical records observed a lower likelihood of reporting pain in those who received an early amputation versus a late amputation (48). In a longitudinal analysis up to five years post injury of US servicemen who sustained a combat injury 2001-2008, 90% of those who sustained an upper extremity injury also had a pain-related diagnosis during the immediate aftermath of the injury (year one) and 37-49% had a pain-related diagnosis in year five (49), however interestingly those who sustained an amputation injury reported significantly less pain compared to those who sustained a non-amputation upper extremity injury (above elbow amputation AOR 0.29 (95%CI 0.09, 0.90); below elbow amputation AOR 0.29 (95%CI 0.11, 0.77)). Personnel who sustained an above elbow amputation were more likely to report cervical pain compared to those who sustained a non-amputation upper extremity injury (OR 4.04 (95%CI 1.66, 9.83)).

Non-amputation injuries

A wide range of injuries fall under the category of non-amputation injuries, the full breadth of which would be impossible to cover in this thesis. In this section I shall discuss some of the more prevalent or severe injury types that might be seen amongst those who deployed to Operation HERRICK, as well as the potential sequalae of these injuries.

Penetrating injuries, defined as injuries that cause penetration that break the skin and cause damage to the underlying tissue, were observed as a result of many of the blast/gunshot injuries experienced in Afghanistan (8, 16). These types of injuries vary in severity, with minor abrasions or lacerations being less likely to cause mortality compared to more extensive injuries, for example gunshot wounds or shrapnel that lodge within the body or leave the body (e.g. with an associated entry and exit wound) (8, 16). These types of injuries often lead to haemorrhage or ischemia, but risk of mortality will ultimately rely on whether major vascular areas (e.g. carotid artery) are injured (50).

High risk areas for mortality from penetrating injuries include to the thoracic region, possibly resulting in airway disruption, pneumothorax injury, haemothorax injury flail chest and cardiac tamponade (51). An examination of penetrating neck injuries of UK military personnel concluded that these types of injuries had high risk of subsequent physical comorbidity and had relatively high risk of mortality (41% mortality related to patients injured by energised fragments to the neck; 78% mortality by gunshot wound if the entry wound was located in the neck) (52, 53). Penetrating injuries to the lower extremities resulted in arterial damage in UK and US military personnel, most often to the posterior tibial artery, superficial femoral artery and popliteal artery, usually from blast injuries (69.7%) but also gunshot wounds (30.3%) (33). In a retrospective review of medical records of UK military personnel admitted to medical facilities at Camp Bastion, approximately 16% sustained penetrating abdominal injuries (54). Injuries to the torso with associated aortic rupture, liver injuries and vascular injuries were prevalent in those who died from their injuries, whereas gastrointestinal and perineal injuries were more prevalent in those who survived. Median NISS among survivors was 38 (IQR 27,52) whereas median NISS among fatalities was 75 (IQR 66,75).

Fractures were also a relatively common injury sustained in Afghanistan (17). Fracture severity ranges from partial fractures (breaks that do not cover the full width of the bone), to complete fractures (breaks that cover the full width of the bone). Closed fractures include fractures of the bone that have no associated break in soft tissue, whereas open fractures have associated soft tissue damage. Typically fractures were experienced as a result of blasts or gunshots, though other mechanisms were also present (e.g. falls, vehicle accidents) (17). Fractures of the extremities were most common in injuries from Iraq/Afghanistan, whilst major fractures such as spinal cord injuries were rarer (4.3 per 10000 person-years amongst US Armed Forces personnel deployed to Iraq/Afghanistan between 2000-2009) but

associated with greater comorbidity and increased health care utilisation compared to other chronic diseases (55, 56).

A study investigating the injury codes registered on the UK military joint theatre trauma registry found that *n*=589 UK military personnel sustained a closed fracture and *n*=941 sustained an open fracture during operations to Iraq/Afghanistan (17). The most common closed fractures included fractures of the tibia (15.8%), fibula (14.4%) and calcaneum (13.6%). The most common open fractures included fractures of the tibia (16.9%) femur (10.3%) and fibula (9.9%). Injured personnel with long bone fractures without amputation had a median of 2 surgical procedures (IQR 1-4). Open fractures were associated with a greater length of hospital stay compared to closed fractures ($p<.001$). In a separate study investigating upper limb fractures, scapula fractures were observed in 44/572 UK military personnel, of which open fractures were most prevalent (54%), comorbid injuries were observed frequently (e.g. lung, head, vascular and nerve injuries), injury severity scores were higher ($p<.0001$) and injuries resulting from blasts required more extensive reconstructive surgery (57). More complex wounds (requiring repeated wound debridement) were associated with sustaining a gunshot injury that did not pass straight through the body or where a bone was fractured (58).

Sequalae of non-amputation injuries

The materials associated with penetrating injuries from Iraq/Afghanistan are often metal, however in the case of injuries from explosive devices, these can be environmental (e.g. stone) (18). Elevated urine metal concentrations have been observed in US military personnel with embedded fragments from Iraq/Afghanistan war-related injuries, the most frequently observed being zinc, tungsten and cobalt (59, 60). It is unknown whether these embedded metal fragments might result in long-term health complications, though animal studies have suggested increased rates of malignant rhabdomyosarcomas in those exposed to embedded tungsten, nickel and iron, and due to the solubility of embedded metals, there is a suggestion that there may be long-term risks to cardiovascular, immune system and neurological health (20).

Combat related gunshot wounds have been reported to have a substantial burden of injury. A median of 3 (IQR 2-5) surgical procedures were conducted per UK military personnel who sustained a gunshot wound (*n*=546) between admission to deployed military surgical facilities and subsequent transfer to RCDM (10). Gunshot wounds can result in significant morbidity including chronic pain, nerve damage and muscle damage alongside mental health

morbidity (61). An investigation into US military personnel injured in Iraq between 2004-2005 suggested that gunshot wounds in particular were associated with increased risk for any mental disorder (defined as any ICD code between 290-319) (AOR 2.70 (95%CI 1.79, 4.06) but not PTSD (AOR 1.49 (95%CI 0.90, 2.46) compared to those who sustained injuries by other non-IED/gunshot wound mechanisms. Injury by IED was not associated with increased risk of PTSD (AOR 1.02 (95%CI 0.65, 1.56) or any mental disorder (AOR 1.21 (95%CI 0.85, 1.71) compared to the same other non-IED/gunshot wound injury mechanism group (62). As discussed earlier, gunshot wounds may result in many types of injuries and is limited as an indicator of injury severity due to the wide range of possible outcomes. Many types of injury, especially genital injury, are under-researched and little to no research exists on the sequalae of these types of injuries (63).

Closed long bone fractures sustained in Iraq/Afghanistan were associated with 11 days (IQR 6-32) of hospital admission, which was significantly shorter in comparison to open long bone fractures (median 24 days (IQR 14-36); $p<.0001$) (17). Closed fractures were associated with a median of 1 (IQR 0-3) surgical procedures compared to 3 (IQR 2-5) for open fractures ($p<.0001$). Non-union fractures (fractures that fail to heal) and avascular necrosis (bone tissue death due to lack of blood supply) are possible outcome of fracture injury. These fractures can result in considerable chronic pain, functional disability and reductions in quality of life (64, 65). More severe injuries, such as injuries with extensive associated soft tissue damage, and injuries with associated subsequent infection are more likely to result in non-union fractures (66) or requiring late amputation (67).

The anatomical region of injury has a considerable impact on the associated sequalae of injury. An analysis of fatal injury versus survived injury among US military personnel found that those who sustained fatal injuries usually had higher severity of injuries in a specific anatomical region along with presence of injuries in multiple other regions (68). The presence of colonic injury (AOR 4.92 (95%CI 1.29,18.64) and number of organs injured (AOR 1.66 (95%CI 1.02, 2.67) have been shown to be significant predictors of post-operative complications/morbidity in Turkish military personnel who sustained high-velocity gunshot injuries to the abdomen (69). Penetrating injuries to the lower extremities resulting in arterial damage from blast-related injuries were associated with greater burden of soft tissue/skeletal injury compared to UK/US military personnel who sustained these types of injuries from gunshot wounds (33).

Severity of combat injury has previously been shown to be associated with poor mental health outcomes in US military personnel deployed to Iraq. Compared to those who sustained minor injuries (Injury Severity Score (ISS) 1-3), those who sustained severe injuries (ISS 16+) had greater odds of receiving any diagnosis of a mental illness (defined as ICD-9 code 290-319) (AOR 5.68 (95%CI 3.00, 10.76) or specifically a PTSD diagnosis (AOR 3.37 (95%CI 1.72, 6.60), though this includes both non-amputation and amputation-related injuries together (62). PTSD has been identified as a possible consequence of traumatic fracture, with a pooled incidence rate of 29% (95%CI 20, 39), though there was notable heterogeneity depending on injury mechanism, injury site and study location (70). Risk factors for subsequent affective disorder following open lower limb fracture include poor social support, pain, low socioeconomic status, and negative affect (71).

Acute pain from injuries was explored in a study of US Armed Forces personnel who sustained a combat injury and were medically evacuated to the Landstuhl Regional Medical Centre (72). In the immediate aftermath of injury (within five days of admission), using a numerical rating scale of pain ranging from 0 (no pain) to 10 (worst pain imagined), personnel reported a mean score of 7.4 during transport to hospital which reduced to a mean score of 3.4 at time of survey. A separate analysis investigating UK combat injured personnel found approximately 30% reported neuropathic pain (e.g. pain resulting from dysfunction of the peripheral or central nervous system) (73).

Psychological injuries

Trauma

Since the inception of the Diagnostics Statistical Manual (DSM), the recognition of the importance of a ‘stressor event’ was noted in several psychological illnesses, however this event has been inconsistently defined across versions of the DSM, from stressors or events “outside the range of usual human experience” (74) to its current iteration of “exposure to actual or threatened death”, “serious injury” or “sexual violence” (75). It is likely that those deployed to Afghanistan, particularly in combat roles, may have been exposed to some of these types of events (76), which is of course especially true for those who sustained a combat injury. Traumatic life events have the potential to inflict significant changes on our perception of the world, ourselves and others. These traumas can be “…permanently encoded in the survivor’s psyche via changes in these basic schemas that reflect some degree of both disillusionment and personal vulnerability” ((77) pg. 30). Survivors of trauma may be

required to reappraise and reconstruct certain life schemas, and the resulting new schemas can have consequences for their physical and psychological health.

Military personnel deployed to Afghanistan may have been exposed to possible/threatened death or serious injury, either to themselves or to friends/colleagues, such as through exposure to IEDs or coming under fire from gunshots or artillery fire (78). In a representative cohort study of UK military personnel deployed to Iraq or Afghanistan, 51.6% of participants who deployed to Afghanistan reported having seen personnel wounded or killed, 16.6% reported having a comrade shot/hit who was near them, 24.6% reported having been in close proximity to an IED, 49.9% reported coming under small arms/RPG fire and 74.2% reported coming under mortar fire/artillery fire/a rocket attack (79). However, this was reflective only of military personnel who deployed to Operation HERRICK between 2006 and 2007. Operational tempo changed over the course of Operation HERRICK, especially as injuries sustained by the UK military increased and peaked in 2010 (2), so the rates of these reported combat exposures have likely increased since the study was conducted.

Post-Traumatic Stress Disorder (PTSD)

One possible consequence of trauma is PTSD. The experienced trauma leaves such an impression that the individual incorporates the trauma into their daily life; perceiving the threat of subsequent trauma in their environment or being unable to process the trauma in line with their moral or general schemas/perceptions regarding their life, e.g. 'people are good' or 'I am safe' (77). Symptoms of PTSD can be categorised in four domains[6]: intrusive thoughts/re-experiencing, avoidance behaviours, emotional numbing and hyperarousal (75, 80). Intrusive symptoms include unwanted re-experiencing of the traumatic event, such as flashbacks or nightmares. Avoidance behaviours include the person making efforts to avoid reminders of the trauma or feelings associated with the trauma. Emotional numbing includes symptoms such as anhedonia or experiencing strong negative emotions such as anger or shame. Hyperarousal symptoms include alterations in arousal, such as hypervigilance or a heightened startle reaction. PTSD is a heterogeneous disorder, with symptoms from these clusters varying in severity and nature from person to person (81).

[6] *It is important to note that in the current DSM-V, some differences exist in the symptom clusters of PTSD. Emotional numbing has been expanded to include negative alterations in cognitions/mood. Additionally, there is a subtype of PTSD including dissociative symptoms. This subtype is not explored as part of this thesis. Discussion of this can be found in chapter 5 and chapter 7.*

Increased rates of PTSD have been observed in UK military personnel deployed to Iraq/Afghanistan, particularly if those personnel were deployed in a combat role (76, 82). In a meta-analysis of US military personnel who deployed to Iraq or Afghanistan, PTSD prevalence was estimated as 23% (83). PTSD is reported in approximately 5% of the UK general population (84), and between 3% to 6% of military personnel who have deployed to Iraq/Afghanistan (82, 85). In a cohort study investigating a representative sample of UK Armed Forces personnel who deployed compared to those who did not deploy to Iraq/Afghanistan, the rate of PTSD was 6%, which significantly rose to 17% when investigating those who deployed in a combat role and had left service (AOR 2.53 (95%CI 1.60, 3.99) (82).

Only one UK paper reports the association between sustaining an injury on deployment to Iraq or Afghanistan and PTSD in the UK military (86). This paper suggests that being evacuated to a UK hospital due to injury was associated with increased odds of reporting PTSD (AOR 4.27 (95%CI 1.80, 10.12)). This study was limited by a small sample size (*n*=89). US data on rates of PTSD amongst those who sustained a combat injury suggests PTSD ranges from 4-58%, including injury types such as thermal injuries, amputations, explosive or gunshot wounds (32, 38, 46, 87-100). However, many studies focus on reporting rates without a suitable comparison group. When comparisons between rates of mental illness were made, they were often made against other injured personnel, e.g. those who sustained a genitourinary injury versus those who sustained a non-genitourinary injury, or those who sustained minor injuries versus severe injuries (62, 99). Therefore, attribution of combat injury to the rates of PTSD are difficult to establish.

Sequalae of PTSD

PTSD is associated with a wide range of physical and mental health conditions. In terms of physical health, PTSD is associated with increased rates of all-cause mortality, Cardiovascular Disease (CVD) and pain disorders (101, 102). Assessment of the Adult Psychiatric Morbidity Survey (APMS) 2007, a representative sample of the English adult population, found that PTSD is associated with increased odds for physical multimorbidity (OR 2.47 (95%CI 1.71, 3.56), with rates of PTSD for those with no physical health conditions at 2.1% and increasing to 5.4% in those with ≥4 physical health conditions (103). Evidence is also present in US veterans that psychiatric conditions, including PTSD, are strong predictors of future physical health comorbidity/multimorbidity (104). Health related quality of life has been observed to be lower amongst US military personnel who sustained a

combat injury and screened positive for PTSD compared to those who did not screen positive for PTSD (9). People with PTSD are also more likely to engage in unhealthy lifestyle factors such as increased alcohol misuse, increased tobacco-use and not engaging in regular physical exercise[7] (105, 106).

In terms of mental health, PTSD has been observed to be a highly heterogenous disorder with high rates of comorbidity with depression, anxiety, negative affect (e.g. increased experience of negative emotions) and other mental illnesses/aspects of poor mental health (e.g. anger, suicidality) (107-110). In a 20-year longitudinal study of Israeli male veterans of the Lebanon War, PTSD with co-morbid depression and co-morbid anxiety (26.7-30.1%) was more common than PTSD (9.3%-11.1%) or PTSD with a singular comorbidity (depression or anxiety) (1.2-4.5%) (111). Veterans in this study who reported triple comorbidity reported poorer psychosocial functioning (e.g. lower occupational performance, family functioning, sexual functioning or social functioning). A study investigating comorbidity between PTSD and major depressive disorder found that, in a representative cohort of US veterans from the national health and resilience in veterans study, comorbidity (3.4%) was more common than PTSD alone (1.7%), and comorbidity was associated with a greater likelihood of suicidality, additional comorbidities (e.g. anxiety disorders, social anxiety) and utilising mental health services (110). PTSD has been observed to have a non-linear association with PTG, which is discussed in the PTG section of this chapter below.

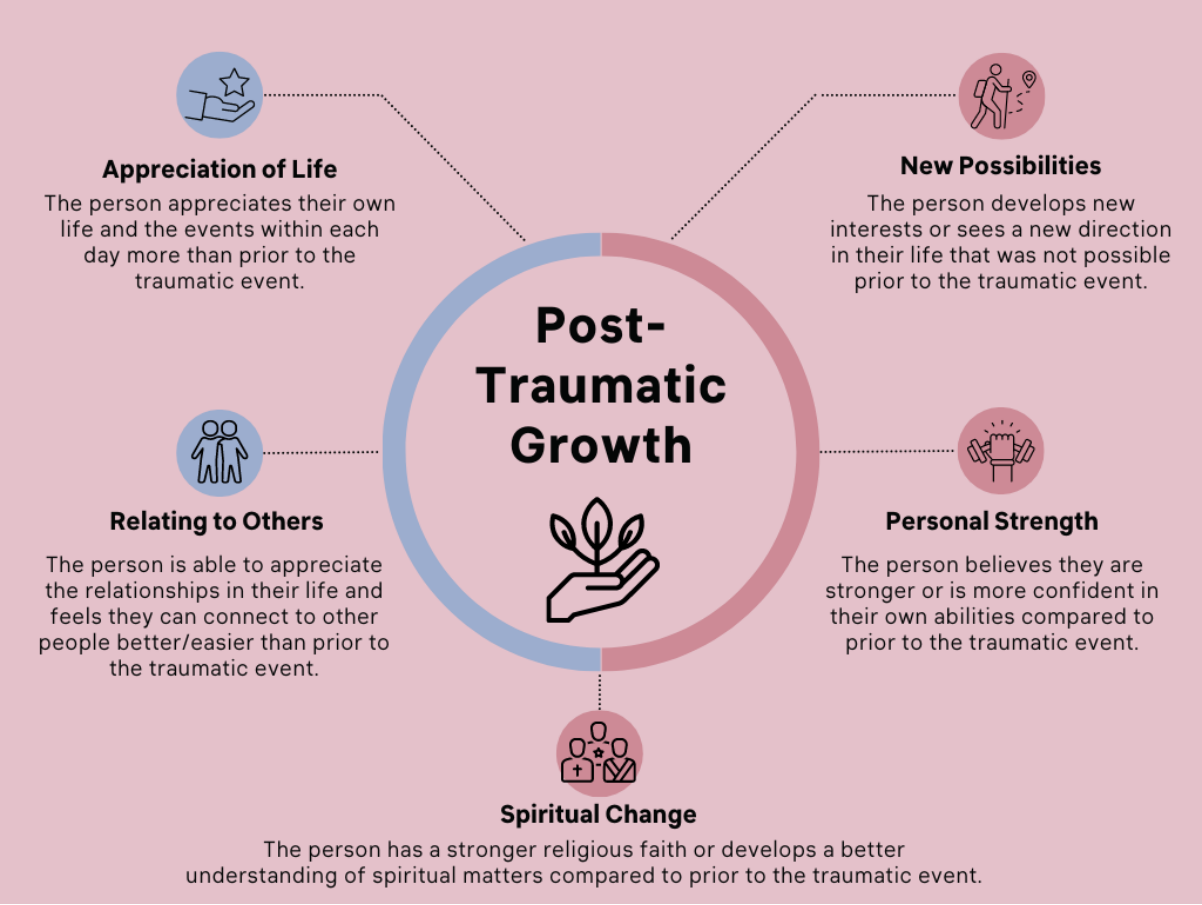
Post-Traumatic Growth (PTG)

Another possible consequence of trauma is PTG. PTG is defined as growth in psychological domains beyond that experienced prior to the trauma (112), thereby being perceived as a positive consequence of trauma. Like PTSD, PTG involves integrating the experience of the trauma into one's life views (i.e. schemas), however instead of replacing schemas such as 'most people are trustworthy' with negative schemas e.g. 'most people are not to be trusted', they are either strengthened or replaced with other positive schemas e.g. 'the people in my life can be trusted' (77, 113). The Post-Traumatic Growth Inventory (PTGI), one of the most used measures of PTG, suggests five factors of PTG; being better able to relate to others,

[7] *A systematic review on PTSD and CVD risk in military personnel who deployed to Iraq/Afghanistan can be found later in this chapter (pg. 51-82).*

perceiving new possibilities in life, appreciation of one's own personal strength, spiritual change and appreciation of life (114) (Chapter 1 Figure 3).

CHAPTER 1 FIGURE 3: THE FIVE FACTORS OF POST-TRAUMATIC GROWTH



Janoff Bulman (2004) proposes three models of PTG: strength through suffering, whereby survivors experience PTG through an understanding of the strength they must possess to have survived; psychological preparedness, whereby survivors experience PTG by now being prepared for future misfortunes, and existential re-evaluation, whereby survivors experience PTG through a new appreciation of one's existence in the world (77). This is not a singular process, whereby the survivor has only positive or negative consequences of trauma, but a process of restructuring and building new psychological domains from the ones proven untrue by the trauma, which can lead to both positive and negative schemas, as evidenced by the fact that PTSD and PTG are not mutually exclusive (115, 116). Indeed, a curvilinear (inverted-u shape) relationship between PTSD and PTG has been noted, whereby as PTSD symptoms increase, so does PTG, up to a point, at which as PTSD symptoms increase, PTG decreases.

Deployment-related PTG has been observed in UK Armed Forces personnel who deployed to Iraq/Afghanistan. In a gender-stratified model, it was found that amongst males, factors associated with reporting a moderate-large degree of PTG (compared to no/very low PTG) included: being a reservist (compared to a regular serving personnel); greater perceived threat of injury or death; greater exposure to a number of different combat experiences; being of lower rank (compared to non-commissioned officer rank); younger age; reporting good/excellent general health (compared to fair/poor health); reporting lower alcohol use and reporting better mental health (117). PTSD was reported to have a curvilinear relationship with PTG. A second paper on a treatment-seeking UK military sample with PTSD found that following treatment for PTSD, personnel were more likely to report PTG, indicating that PTG can be elicited from intervention (118).

No data currently exists on the experience of PTG amongst UK military personnel who sustained a combat injury. Amongst US military personnel who sustained an amputation injury in Iraq/Afghanistan, the mean score on the PTGI was 59 (possible range 0-105; whereby a higher score indicates greater PTG), which represents at least a moderate amount of growth in this sample (119).

Sequalae of PTG

PTG is increasingly the focus of scientific inquiry with regard to its relationship with physical health, however it still remains under-researched and only a limited amount of data is available on associations between PTG and physical health. It has been observed amongst those with serious medical conditions, (e.g. HIV/AIDS, cardiac disease, multiple sclerosis, rheumatoid arthritis), PTG is associated with lower rates of depression, anxiety and pain (115). Among UK Armed Forces personnel deployed to Iraq/Afghanistan, PTG is associated with better perceived overall health, lower rates of CMD and lower alcohol use (117). Those who experience PTG have also been found to report greater quality of life amongst groups such as cancer survivors, those living with serious medical conditions and US military ex-serving personnel with serious injuries/illnesses (115, 120, 121).

Common Mental Disorders (CMD)

CMD in this thesis refer to depression and/or anxiety disorders. Whilst these disorders do not require a traumatic event to occur, CMD are possible consequences of trauma (122). The DSM-V defines depression as an individual experiencing some/all of the following symptoms regularly over the last two weeks: depressed mood; anhedonia; change in appetite; restlessness or lethargy; negative self-perceptions; diminished ability to concentrate and

suicidal ideation (123). The DSM-V defines generalised anxiety disorder as experiencing some/all of the following symptoms: excessive anxiety or worry; inability to control anxiety/worry; restlessness; fatigue; poor concentration; irritability; muscle tension and sleep disturbance (123).

Whilst rates of CMD are generally accepted to be similar between the UK military and the UK general population, it is noted that odds of reporting CMD are increased in those who deployed to Iraq/Afghanistan in a combat role and left service compared to those who deployed in a combat service support role and left service (AOR 1.70 (95%CI 1.28, 2.41)) (82).

Only one UK paper exists on the association between combat injury and CMD (86). This paper suggests that being evacuated to a UK hospital due to injury in Afghanistan was associated with increased odds of reporting probable CMD (AOR 2.79 (95%CI 1.41, 5.51), though as noted above this study is limited by a small sample size (*n*=89). Amongst US military personnel who sustained a combat injury, rates of CMD range from 3-58% (66-70). Traumatic amputation worldwide has been associated with rates of depression between 20-63% and rates of anxiety between 25-57% (43, 124).

Sequalae of CMD

Experiencing a mental illness is bidirectionally associated with physical disorders (125). For example, a person with depression is more likely to become obese, and those who are obese are more likely to become depressed (126). Furthermore, research has shown that cardiovascular risk factors, such as smoking or high Body Mass Index (BMI), are associated with a higher risk of subsequent depression in young people (127). Data from the APMS 2014 dataset suggests that the prevalence of any five physical chronic conditions (specifically epilepsy, cancer, diabetes, asthma or high blood pressure) increases as CMD symptom severity increases (128). In samples with associated physical health problems (e.g. heart failure, diabetes, cancer), CMD is associated with increased mortality risk or may be a marker of more severe disability from the comorbid physical condition (129-131). High levels of impairment have been noted amongst those with CMD, particularly with regards to mental health and social functioning, but also overall quality of life and physical functioning (132, 133).

Mental health multimorbidity

It is recognised that PTSD and CMD may be experienced simultaneously, and when this is the case, the experience of both PTSD and CMD symptoms is more severe, representing a cumulative adverse effect with increased psychological burden beyond that of PTSD alone or CMD alone (110). Whilst PTG and PTSD share etiological pathways, and thus can be experienced simultaneously, these pathways do not necessarily exist with PTG and CMD. As discussed above, CMD can exist without a preceding traumatic event (122), which is not true of PTG. It would be unlikely that a person can experience aspects of PTG such as appreciation of life alongside aspects of depression, e.g. anhedonia. Therefore, comorbidity of PTG and CMD is not thought to be common, which is supported by the fact that UK military personnel who deployed to Iraq/Afghanistan and reported a large degree of PTG were less likely to report CMD compared to those who reported no/a very low degree of PTG (117).

Mental health multimorbidity among those with combat injuries has not been specifically investigated, however one study has investigated latent classes (e.g. clusters of disorders) of physical and mental health conditions amongst Iraq/Afghanistan US military personnel/veterans (134). Six clusters were identified: cluster one included personnel experiencing the polytrauma clinical triad (which is a pattern of injury/illness that includes Traumatic Brain Injury (TBI), PTSD and pain) along with chronic disease; cluster two included the polytrauma clinical triad only; cluster three included mental health (PTSD, depression, anxiety, or bipolar disorder) and substance abuse; cluster four included sleep problems, amputation and chronic disease; cluster five included pain and moderate PTSD symptoms and cluster six referred to the relatively healthy. The relatively healthy cluster accounted for the majority of participants in the study (53.3%), followed by the mental health and substance abuse cluster (23.6%).

Mental health and cardiovascular health

This thesis will explore causal mechanisms between mental health and physical health including the Hypo-Pituitary Adrenal Axis (HPA), Sympathetic Adrenal System (SAS), metabolic effects including the metabolic syndrome and lifestyle behaviours (102). Specifically, the relationship between PTSD and PTG with CVD and cardiovascular risk factors will be explored.

Hypo-Pituitary Adrenal Axis

One of the most prominent theorised pathways between mental and physical health utilises the processes involved in activation of the HPA (135). The HPA is a primary stress response operator that manages systems across the body in response to environmental stimuli, with the purpose of ensuring survival. This response is maintained through homeostasis, ensuring that the system is activated in times of stress and deactivated once the stressor is no longer present. The primary hormone that affects physical health systems from the HPA is cortisol. Cortisol is produced with the main aim of increasing blood sugar glucose levels, releasing energy from fat deposits so they can be used to react to the current stressor. Cortisol also may have other wide-ranging effects, including influencing cardiovascular risk factors such as cardiac function, inflammatory reactions and lipid abnormalities (136).

Cortisol dysregulation, for example cortisol excess, has many negative influences on the cardiovascular system. Cortisol dysregulation is associated with higher blood pressure, increased obesity indicators (such as increased BMI, increased waist-hip ratio, and android fat), blood glucose, greater insulin resistance, higher levels of triglycerides, higher levels of total cholesterol and Low-Density Lipoproteins (LDL; also known as 'bad' cholesterol), and lower levels of High-Density Lipoproteins (HDL; also known as 'good' cholesterol) (137). Dysregulated cortisol excretion can be difficult to examine, as circulating cortisol may be normal or low even when cortisol excretion is increased, likely due to differences in the potency of cortisol at tissue level (138). People with PTSD have been shown to have dysregulated cortisol responses and muted expression of genes related to glucocorticoid receptor sensitivity (139, 140). PTG has been observed to be associated with healthier endocrine functioning, specifically lower cortisol levels in cancer patients (141). The lower cortisol levels observed have been theorised as being the reason why cancer, HIV and myocardial infarction survivors who experience PTG have better survival rates in comparison to those who do not experience PTG (115).

Sympathetic Adrenal System (SAS)

Like the HPA, the SAS reacts to environmental stimuli by connecting the sympathetic nervous system to the adrenal medulla, resulting in adrenaline and noradrenaline secretion. This system is primarily used in the fight or flight response, though has many other functions as well. For example, noradrenaline is involved in the processing of emotionally-arousing memories in the brain (142). Excessive SAS activation (hyperactivity) can have

direct and indirect effects on CVD risk factors through dysregulated adrenaline and noradrenaline secretion, including effects on blood pressure, cardiac function, endothelial functioning, platelets and metabolic function (135, 143, 144). PTSD symptoms such as hyperarousal and re-experiencing are linked to hyperactivity of noradrenaline (145). No known studies have investigated the links between adrenaline and PTG**.**

Metabolic syndrome: Obesity, diabetes, hypertension and dyslipidaemia

Metabolic syndrome refers to a series of CVD risk factors that may cluster together, including obesity, increased insulin resistance or blood glucose disorders (e.g. diabetes), hypertension and dyslipidaemia. Each of these risk factors of the metabolic syndrome is associated with greater risk of developing CVD (146, 147), and the combination of these risk factors as observed in the metabolic syndrome carries with it an even greater risk of subsequent CVD (148, 149). There are system overlaps between HPA and SAS dysregulation and the metabolic syndrome (150), and it is likely that dysregulated HPA or SAS play a part in the development of the metabolic syndrome. Those with PTSD have been shown to be at increased risk of metabolic syndrome (151). No known studies have investigated the link between PTG and metabolic syndrome, however links exist between PTG and individual aspects of the metabolic syndrome (115, 152-154).

Behavioural mechanisms

Smoking

Smoking tobacco is a well-established independent risk factor for CVD (155). The mechanisms by which smoking increases CVD risk are wide ranging and include, but are not limited to; increased blood pressure, increased resting heart rate, vascular inflammation and dyslipidaemia (156). Increased smoking has been observed amongst those with PTSD (157). Few studies exist on associations between PTG and smoking, and what literature does exist mostly focusses on PTG in individuals with serious medical conditions (115, 158), which suggest mixed evidence exists for a link between PTG and smoking. A study investigating the associations between health-related behaviours and PTG amongst UK military personnel who deployed to Iraq and/or Afghanistan found that there was no significant association between experiencing a moderate/large degree of PTG and number of cigarettes smoked per day (117).

Obesity

Obesity is an independent risk factor of CVD and refers to excess accumulation of body fat. There are many different measures of obesity, including total body weight, waist/hip ratio (the circumference of the waist/circumference of the hips), android/gynoid ratio (distribution of fat from the android region/gynoid region), and visceral adipose tissue (hormonally activated fat from the abdominal region) (159). The mechanisms by which obesity increases CVD risk include, but are not limited to; diabetes, dyslipidaemia, hypertension, inflammation and insulin resistance (159, 160). Increased visceral adipose tissue, a specific indicator of obesity which has been found to be a risk factor of CVD independent of total body mass, is linked to bioactive responses such as inflammation, diabetes, dyslipidaemia, haemodynamic functioning and especially insulin resistance (161). PTSD is linked to increased rates of obesity (106). Those who experience PTG have been shown to be more likely to exhibit healthier behaviours such as exercise, better diet and greater attention to physical health (115, 117), though there seems to be a lack of studies investigating obesity rates amongst those who experience PTG.

Physical activity

Physical activity is an independent risk factor of CVD (162). Increased physical activity is associated with better performance of the cardiovascular and pulmonary systems. The mechanisms by which physical activity decreases cardiovascular risk include, but are not limited to: lipid concentrations, blood glucose concentrations, and decreased blood pressure (163-165). Those with PTSD have been shown to be less likely to engage in physical activity (106) whereas those who experience PTG have been shown to be more likely to engage in physical activity (115).

Post-Traumatic Stress Disorder and cardiovascular health

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The association between PTSD and cardiovascular disease and its risk factors in male veterans of the Iraq/Afghanistan conflicts: A systematic review

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Abstract

Military personnel with Post-Traumatic Stress Disorder (PTSD) can experience high levels of mental and physical health comorbidity, potentially indicating a high level of functional impairment that can impact on both military readiness and later ill-health. There is strong evidence to implicate PTSD as a contributory factor to Cardiovascular Disease (CVD) among serving personnel and veterans. This systematic review focusses on the association between PTSD and cardiovascular disease/risk factors in male, military serving and ex-serving personnel who served in the Iraq/Afghanistan conflicts. PUBMED, MEDLINE, PILOTS,

EMBASE, PSYCINFO and PSYCARTICLES were searched using PRISMA guidelines. Three hundred and forty-three records were identified, of which twenty articles were selected. PTSD was positively associated with the development of CVD, specifically circulatory diseases, including hypertension. PTSD was also positively associated with the following risk factors: elevated heart rate, tobacco use, dyslipidaemia and obesity. Conflicting data is presented regarding heart rate variability and inflammatory markers. Future studies would benefit from a standardised methodological approach to investigating PTSD and physical health manifestations. It is suggested that clinicians offer health advice for CVD at an earlier age for ex-/serving personnel with PTSD.

Keywords: Cardiovascular diseases; Stress Disorder, Post-Traumatic; Military personnel; Iraq; Afghanistan

Introduction

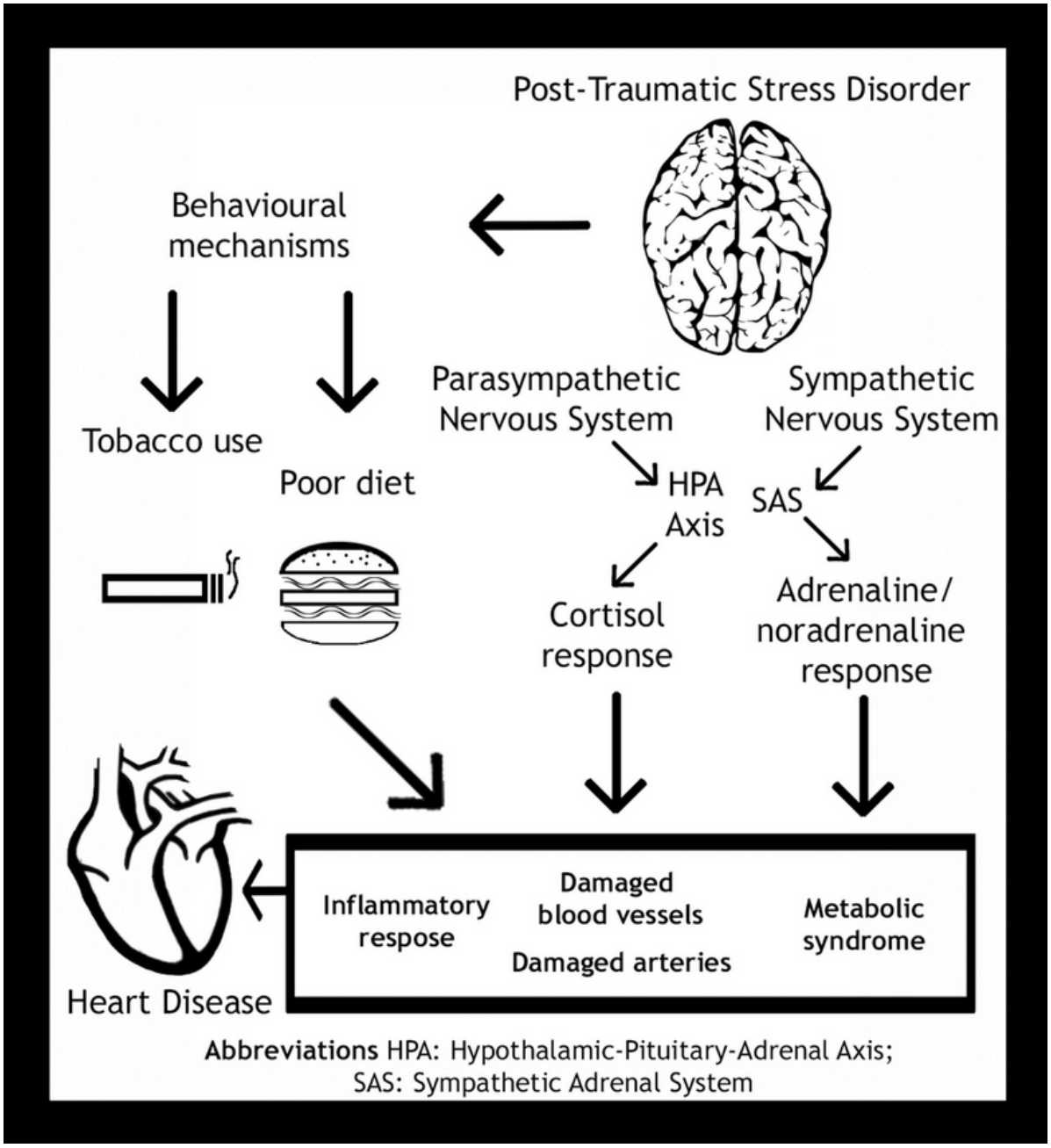
PTSD in the military

Estimates of Post-Traumatic Stress Disorder (PTSD) in the US Armed Forces vary widely, from 4% to 23% of military personnel who have deployed to Iraq/Afghanistan (83, 85). In the UK Armed Forces, around 6% report symptoms of PTSD (82). PTSD has a high level of comorbidity with other mental health conditions (108) and physical health conditions (101, 166), though the latter are often overlooked. There is increasing evidence to suggest that PTSD is associated with elevated rates of Cardiovascular Disease (CVD) (167, 168).

Biological and behavioural mechanisms of PTSD affecting CVD

The biological mechanisms that link PTSD to CVD are numerous and complex (102). This paper will explain some of the more well-established biological mechanisms to facilitate the conceptualisation of the link between mental health and CVD through a brief description of the biological mechanism, how it affects CVD risk factors and how it is linked to PTSD (Chapter 1 Figure 4).

Chapter 1 Figure 4: PTSD and CVD



Hyper Pituitary Adrenal Axis (HPA Axis)

The HPA Axis is a primary stress response operator that manages systems across the body in response to environmental stimuli, with the purpose of ensuring survival (135). This response is maintained through homeostasis, ensuring that the system is not active for prolonged periods of time. The primary hormone that affects physical health systems from the HPA Axis is cortisol. Cortisol is produced with the main aim of increasing blood sugar glucose levels, though also may have other wide-ranging effects, including influencing cardiovascular

risk factors such as cardiac function, inflammatory reactions and lipid abnormalities (136). PTSD populations have been shown to have dysregulated cortisol responses and muted expression of genes related to glucocorticoid receptor sensitivity (140, 169).

Sympathetic Adrenal System (SAS)

Like the HPA Axis, the SAS reacts to environmental stimuli by connecting the sympathetic nervous system to the adrenal medulla situated in the brain, resulting in adrenaline and noradrenaline secretion. Excessive SAS activation (hyperactivity) can have direct and indirect effects on CVD risk factors through dysregulated adrenaline and noradrenaline secretion, including effects on blood pressure, cardiac function, endothelial functioning, platelets and metabolic function (135, 143, 144). PTSD symptoms such as hyperarousal and re-experiencing are linked to hyperactivity of noradrenaline (145).

Imbalance of autonomic systems: Heart Rate Variability (HRV)

HRV refers to the variability in cardiac inter-beat intervals over time. This is thought to be a good representation of sympathetic and parasympathetic impulses on cardiovascular systems, as well as homeostatic control from the hypothalamus, limbic system and brainstem (135).Whilst high HRV is associated with a healthy autonomic response, low HRV reflects hyperactivity or hypoactivity of the sympathetic or parasympathetic response (170). Low HRV is associated with CVD (170, 171). People suffering from PTSD have also been shown to report lower HRV (172-174).

Inflammatory responses

An inflammatory response refers to the body's reaction to foreign pathogens, including disease or infection. Cytokines, the gene-expression of cells to stimulate an inflammatory response, can be expressed in both pro-inflammatory (to elicit an inflammatory response) and anti-inflammatory (to stop an inflammatory response) (175). Inflammatory disease occurs when a dysregulated inflammatory response attacks normal bodily tissue, as can be observed in the arterial lesions associated with atherosclerosis (176-179). PTSD is known to be associated with Interleukin-6 (IL-6), Interleukin-1β (IL-1β), Tumor Necrosis Factor-α (TNFα) and Interferon-γ (IF-γ) cytokines (180) through which heart disease and diabetes can result (181-186).

Metabolic syndrome: Obesity, diabetes, hypertension and dyslipidaemia

Metabolic syndrome refers to a series of CVD risk factors that often cluster together, including obesity, insulin resistance (e.g. diabetes), hypertension and dyslipidaemia. Each risk factor is associated with subsequent CVD (160, 182, 187), and the combination observed in metabolic syndrome carries with it an even greater risk of subsequent CVD (149). Those that suffer from PTSD have been shown to be at increased risk of metabolic syndrome (151).

Behavioural mechanisms

Tobacco-use and poor diet are both well-established risk factors for diabetes (188) and CVD, including atherosclerosis, coronary heart disease and aortic aneurysm (160, 189, 190). Behaviours such as smoking and poor diet have all been shown to be higher in US veterans/serving personnel with PTSD compared to those without PTSD (191).

PTSD and CVD in the Armed Forces community

To the authors' knowledge, one systematic review and one meta-analysis have been conducted in the past decade regarding the physical health comorbidities associated with PTSD (101, 166). The meta-analysis suggested that veteran samples with PTSD reported significantly more cardio-respiratory symptoms including heart disease (weighted effect size 0.17 (95%CI 0.12, 0.22) when compared to civilian samples (101). The length of time it takes for these physical symptoms to manifest as a result of PTSD is unknown. The current review builds upon this work by examining the evidence for the mechanisms by which PTSD might impact on heart disease by focussing only on a more recent deployment with an established research base: Iraq/Afghanistan deployed ex-/serving personnel.

Objective

The aim of this systematic review is to investigate the association between CVD and CVD risk factors within ex-/serving personnel with PTSD who deployed to Iraq/Afghanistan.

Methods

EMBASE, MEDLINE, PSYCARTICLES, PSYCINFO, PUBMED and PILOTS were searched in December 2018 with a combination of search terms (supplementary material 1) according to PRISMA guidelines (192). The search contained key words relating to: PTSD AND cardiovascular outcome/risk factor AND occupation within the armed forces AND Iraq/Afghanistan deployment. Mesh terms were explored to find additional search terms.

Review criteria included that articles: were published between 2001 (the beginning of the Iraq war) and December 2018; were written in English; consisted of empirical research

examining the association between PTSD and cardiovascular outcomes/risk factors; reported on a male population or presented statistics stratified by sex; included personnel deployed to Iraq/Afghanistan and provided details of prevalence rates or univariable/multivariable associations between PTSD and cardiovascular outcomes/risk factors. Exclusions were applied during title/abstract review and full text review (Chapter 2 Figure 5).

Stroke/cerebrovascular outcomes were also excluded due to their high correlation with head injuries (193). Inflammatory markers were limited to markers known to be both associated with PTSD and CVD (180, 181, 183-186).

Reference lists were checked for additional articles. Where necessary statistical information was lacking, an attempt was made to contact corresponding authors. If necessary information was not provided by the corresponding author, the article was excluded from analysis.

DD conducted a full title and abstract review. SE reviewed 12.5% of the studies at both title and abstract (n =43) and full text review (n =10) stages. The Kappa reliability score between DD and SE was 0.96, indicating a strong level of inter-rater agreement.

A quality analysis was conducted by DD and SE on all included articles based on the National Heart, Lung and Blood Institute (NHLBI) study quality assessment tools (194). Articles were then defined as ‘good’, ‘fair’ or ‘poor’ based on the qualities addressed in the NHLBI tool. DD and SE discussed any disagreements in their quality analysis and adjusted accordingly (Chapter 1 Supplementary Materials 2).

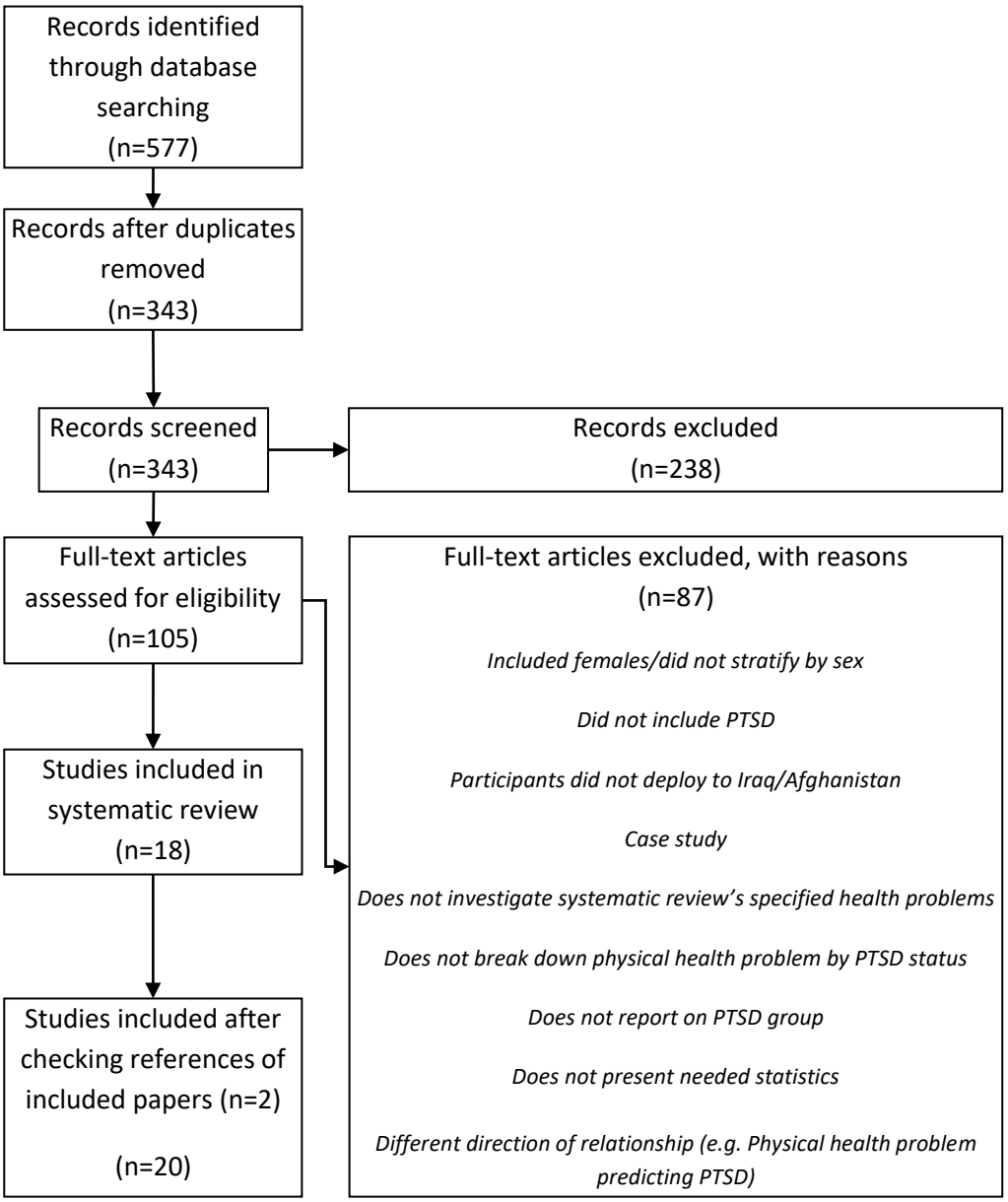
Data Extraction

Results were generated by extracting study information regarding the study methodology including: author; year of publication; sample size; recruitment sample; cardiovascular outcome; method of measuring PTSD; method of analysing the CVD outcome/risk factor of interest and length of time since diagnosis of PTSD (supplementary material 3).

One article presented the raw data for each of 28 participants (195), this data was extracted into Microsoft Excel (2016 MSO) to generate means and standard deviations of both clinical and demographic values. Three articles (196-198) appear to report on the same population pool at different time points. All were included as they either a) explicitly reported being a replication study on a different sample within that population or b) reported on different health outcomes.

All statistics reported relating to PTSD and a cardiovascular outcome/risk factor were extracted (supplementary material 4). Significance was defined as $p<.05$. Health data was grouped into risk factors and outcomes. Risk factors included: tobacco use, weight, diabetes, blood pressure, heart function and inflammatory markers. Forest plots were created using metadata viewer (199). Pooled estimates were created by multiplying each study estimate by the study sample size, then dividing the sum of these values by the sum of the sample sizes, minus the number of studies. A pooled Standardised Mean Difference (SMD) for daytime heart rate and Risk Ratio (RR) for tobacco use was estimated in STATA SE 15.0 using the metan function and a random effects model for all studies that reported on an exposed (PTSD) and control (non-PTSD) group.

Chapter 1 Figure 5: Prisma Systematic Review Flow Diagram



Results

Twenty articles met the inclusion criteria. Articles were published between 2008 and 2018 and were based on US samples. Sample sizes ranged from *n* =10 to *n* =436932, with only seven studies having a sample size >200. Seven studies analysed medical records, 12 were cross-sectional and one was case-control. For the purposes of this review, 18 of the articles had a non-PTSD control sample. Five articles were assessed as poor quality, ten as fair and five as good.

Sample and study characteristics of all included articles are displayed in Chapter 1 Table 2. Positive, negative and non-statistically significant associations are presented for risk factors (Chapter 1 Table 3) and cardiovascular outcomes (Chapter 1 Table 4). Statistical outcomes/effect estimates can be found in Chapter 1 Supplementary Materials 4.

CHAPTER 1 TABLE 2: METHODOLOGICAL SUMMARIES OF INCLUDED STUDIES

Author	Type of study	Total N (PTSD N)	Age in years at recruitment	Recruitment location	Quality score
Kirby et al., 2008 (200)	Cross-sectional	90 (90)	PTSD+ current smokers M 28.34 (SD 7.11) PTSD+ non-smokers M 34.82 (SD 9.83)	Clinical: VA Outpatient PTSD Clinic	Poor
Cohen et al., 2009 (201)	Analysis of medical records	303223 (72773)	M 31.00 (SD 9.00)	Clinical: VHA	Fair
Tan et al., 2009 (195)	Cross-sectional	28 (12)	PTSD+ M 30.63 (SD 6.76) PTSD- M 33.08 (SD 9.95)	Clinical: polytrauma medical centre	Poor
Ginsberg et al., 2010 (202)	Cross-sectional	10 (5)	PTSD+ M 29.40 (SD 2.50) PTSD- M 32.20 (SD 2.60)	Clinical: VA mental health outpatient medical centres	Poor
Frayne et al., 2011 (203)	Analysis of medical records	12831 (3503)	PTSD+ <30: 51.80% ≥30: 48.20% PTSD-	Clinical: VHA outpatient care	Good

Author	Type of study	Total N (PTSD N)	Age in years at recruitment	Recruitment location	Quality score
			<30: 60.90% ≥30: 39.10%		
Nazarian et al., 2012 (204)	Analysis of medical records	62496 (22311)	<25: 18.50% ≥25: 81.50%	Clinical: VHA primary care	Fair
Agorastos et al., 2013 (205)	Cross-sectional	15 (7)	PTSD+ M 26.30 (SD 4.00) PTSD- M 30.90 (SD 10.60)	NR	Fair
Maguen et al., 2013 (206)	Analysis of medical records	436932 (167937)	PTSD+ M 30.90 (SD 8.69) PTSD- M 32.70 (SD 9.74)	Clinical: VA healthcare	Fair
Paulus et al., 2013 (207)	Analysis of medical records	186 (88)	PTSD+ M 26.00 (NR) PTSD- M 32.00 (NR)	Clinical: VHA outpatient psychiatry	Poor
Caska et al., 2014 (208)	Cross-sectional	65 (32)	PTSD+ M 32.70 (range 24-53) PTSD- M 34.70 (range 23-49)	Mixed: VA medical centres and post-deployment workshops	Fair
Lindqvist et al., 2014 (198)	Cross-sectional	102 (51)	PTSD+ M 34.10 (SD 8.70) PTSD- M 33.70 (SD 9.00)	Mixed: VA mental health services; other regional veterans service organisations; National Guard; Reservist agencies and general community.	Good
Ramaswamy et al., 2015 (209)	Cross-sectional	11 (11)	M 28.00 (SD 2.60)	Clinical: Outpatient VA medical centre	Poor

Author	Type of study	Total N (PTSD N)	Age in years at recruitment	Recruitment location	Quality score
Bersani et al., 2016 (210)	Cross-sectional	139 (67)	PTSD+ (group 1) M 33.07 (SD 7.88) PTSD- (group 1) M 32.93 (SD 8.44) PTSD+ (group 2) M 31.04 (SD 5.87) PTSD- (group 2) M 30.63 (SD 5.75)	Mixed: VHA, medical centres, national guard, reservist agencies and general community	Fair
Japuntich et al., 2016 (211)	Cross-sectional	1074 (NR)	NR	General community: VHA Environmental Epidemiology Service roster	Poor
Lerman et al., 2016 (212)	Cross-sectional	21 (10)	PTSD+ M 28.90 (SD 8.80) PTSD- M 28.50 (SD 7.00)	General community: greater San Diego area	Fair
Blessing et al., 2017 (196)	Case-control	166 (83)	PTSD+ M 33.00 (SD 7.70) PTSD- M 32.50 (SD 8.00)	Mixed: VA mental health services; other regional veterans service organisations; National Guard; Reservist agencies and general community	Fair
Burg et al., 2017 (213)	Analysis of medical records	194319 (69583)	Median 27.90 (IQR 24.40, 37.60)	Clinical: VA roster	Fair

Author	Type of study	Total N (PTSD N)	Age in years at recruitment	Recruitment location	Quality score
Lindqvist et al., 2017 (197)	Cross-sectional	61 (31)	PTSD+ M 31.20 (SD 5.50) PTSD- M 30.80 (SD 5.60)	Mixed: VA mental health services; other regional veterans service organisations; National Guard; Reservist agencies and general community	Good
Ray et al., 2017 (214)	Cross-sectional	70 (70)	PTSD+ M 32.10 (SD 6.70) PTSD+AUD M 30.52 (SD 5.40)	Mixed: VHA mental health clinics and general community	Fair
Buta et al., 2018 (215)	Analysis of medical records	214908 (82944)	Median 28.90 (IQR 24.70, 39.70)	Clinical: VA healthcare users with PTSD	Good

Abbreviations: AUD=Alcohol Use Disorder, IQR=Inter Quartile Range, M=Mean, NR=Not Reported, PTSD=Post Traumatic Stress Disorder, SD=Standard Deviation, VA=Veterans Administration, VHA=Veterans Health Administration,

CHAPTER 1 TABLE 3: ASSOCIATIONS BETWEEN PTSD AND SUBSEQUENT CARDIOVASCULAR RISK FACTORS

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
Risk factor: Diabetes			
Diabetes (NR)	Frayne et al., 2011 (203)* Cohen et al., 2009 (201)*		Bersani et al., 2016 (210) Cohen et al., 2009 (201)**
Risk factors: Cardiac haemodynamics			
Blood Pressure: Diastolic *(NR)*	Paulus et al., 2013 (207)*		Blessing et al., 2017 (196)*
Blood Pressure: Systolic *(NR)*	Paulus et al., 2013 (207)*		Blessing et al., 2017 (196)*
Heart Rate *(Electrocardiogram: 24 hour)*	Agorastos et al., 2013 (205)*		
Heart Rate *(Electrocardiogram: day time)*	Blessing et al., 2017 (196)*		Agorastos et al., 2013 (205)*
Heart Rate *(Electrocardiogram: night time)*	Agorastos et al., 2013 (205)*		

Measure (Measurement type)	**Significant Positive Associations[1]**	**Significant Negative Associations[1]**	**Non-Significant Associations[1]**
Heart Rate *(NR)*	Paulus et al., 2013 (207)		
Heart Rate Variability *(Electrocardiogram: various methodologies)*	Agorastos et al., 2013 (205)* Low Frequency/High Frequency *night*	Agorastos et al., 2013 (205)* Normal to Normal Intervals *24 hour*	Agorastos et al., 2013 (205)* Ray et al., 2017 (214) Other facets of HRV (supplementary material 4)
Risk Factors: Inflammatory Markers			
C-Reactive Protein *Latex-enhanced immunoturbidimetric assay)*	Blessing et al., 2017 (196)*		
Interferon-Gamma *(High-sensitivity multiplexed sandwich immunoassay)*	Lindqvist et al., 2014 (198)*		Lindqvist et al., 2017 (197)*
Interleukin-1 *(High-sensitivity multiplexed sandwich immunoassay)*			Lindqvist et al., 2014 (198)*

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
Interleukin-1β *(Multi cytokine array with electrochemiluminescence platform)*			Lerman et al., 2016 (212)
Interleukin-6 *(High-sensitivity multiplexed sandwich immunoassay)*			Blessing et al., 2017 (196)*
Interleukin-10 *(High-sensitivity multiplexed sandwich immunoassay)*			Lindqvist et al., 2014 (198)* Lindqvist et al., 2017 (197)* Lerman et al., 2016 (212)
Tumour Necrosis Factor-Alpha *(High-sensitivity multiplexed sandwich immunoassay)*	Blessing et al., 2017 (196)*		
Risk Factors: Lipids			
Dyslipidaemia *(ICD-9)*	Cohen et al., 2009 (201)*		
Hyperlipidaemia *(ICD-9)*	Frayne et al., 2011 (203)*		

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
Cholesterol *(Radioimmunoassay)*			Blessing et al., 2017 (196)*
High-Density Lipoprotein *(Radioimmunoassay)*			Blessing et al., 2017*
Triglycerides *(Radioimmunoassay)*	Blessing et al., 2017 (196)*		
Risk factor: Tobacco use			
Changes in smoking habits post-deployment (Survey)			Japuntich et al., 2016 (211)
Tobacco use (Survey)	Cohen et al., 2009 (201)* Lindqvist et al., 2014 (198) Lindqvist et al., 2017 (197)		Ray et al., 2017 (214)
Risk factor: Weight			

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
BMI *(NR)*	Blessing et al., 2017 (196) Buta et al., 2018 (215)*		Agorastos et al., 2013 (205)
Obese/Overweight *(ICD-9)*	Frayne et al., 2011 (203)* Nazarian et al., 2012 (204)*		
Weight gain over time *(NA)*	Buta et al., 2018 (215)* Maguen et al., 2013 (206)*		

[1] Multivariable analysis is presented in this table unless an article did not present multivariable analysis, in which case the univariable analysis is presented. Significance p=<.05.

*Multivariable analysis

**Cohen et al., 2009 reported on two multivariable models, the second of which (represented here) used number of primary care visits as a method of reducing ascertainment bias.

Abbreviations: ICD: International Classification of Disease, Ln: log-transformed, NA; Not Applicable, NR: Not Reported

CHAPTER 1 TABLE 4: ASSOCIATIONS BETWEEN PTSD AND SUBSEQUENT CARDIOVASCULAR DISEASES

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
Circulatory Diseases			
Circulatory diseases *(ICD-9)*	Frayne et al., 2011 (203)* Nazarian et al., 2012 (204)*		
Coronary atherosclerosis, other heart disease *(ICD-9)*	Frayne et al., 2011 (203)*		
Hypertension *(ICD-9)*	Cohen et al., 2009 (201)* Frayne et al., 2011*		Bersani et al., 2016 (210)
Hypertension event *(diagnosis of hypertension (ICD-9) and/or prescription of antihypertensive medication and/or BP in hypertensive range)*	Burg et al., 2017 (213)*		
Hypertension with complications, secondary hypertension *(ICD-9)*			Frayne et al., 2011 (203)*
Peripheral and visceral atherosclerosis *(ICD-9)*	Frayne et al., 2011 (203)*		

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]
Pulmonary heart disease *(ICD-9)*	Frayne et al., 2011 (203)*		
Heart disease			
Acute myocardial Infarction *(ICD-9)*	Frayne et al., 2011 (203)*		
Congestive heart failure (non-hypertensive) *(ICD-9)*			Frayne et al., 2011 (203)*
Other cardiovascular diseases			
Other and ill-defined heart disease *(ICD-9)*			Frayne et al., 2011 (203)*
Aortic, peripheral and visceral artery aneurysms *(ICD-9)*			Frayne et al., 2011 (203)*
Aortic, peripheral and arterial embolism or thrombosis *(ICD-9)*	Frayne et al., 2011 (203)*		

Measure (Measurement type)	Significant Positive Associations[1]	Significant Negative Associations[1]	Non-Significant Associations[1]

[1] Multivariable analysis is presented in this table unless an article did not present multivariable analysis, in which case the univariable analysis is presented.

Significance *p*=<.05.

*Multivariable analysis

Abbreviations: ICD: International Classification of Diseases; NR: Not Reported

Cardiovascular results

Risk factors

Diabetes

Diabetes status was reported in four articles (201, 203, 204, 210)) (

Chapter 1 Table 3). Two articles used multivariable analysis (201, 203). Both articles reported significantly higher prevalence of diabetes in PTSD+ samples compared to control samples, though one article's association became non-significant when accounting for ascertainment bias (201).

Cardiac Haemodynamics: Blood Pressure/Hypertension

Blood pressure results were reported within seven articles (196, 201, 203, 204, 207, 208, 213) (

Chapter 1 Table 3) Two studies used multivariable analysis to examine differences between PTSD+ and control groups for DBP/SBP. One reported significantly higher mean SBP and DBP in PTSD+ compared to control samples (207) and one article reported borderline/non-significant differences (Blessing et al., 2017). Three studies used multivariable analysis to investigate the association between PTSD and hypertension, and all found a significantly higher prevalence of hypertension in PTSD+ samples (201, 203, 213).

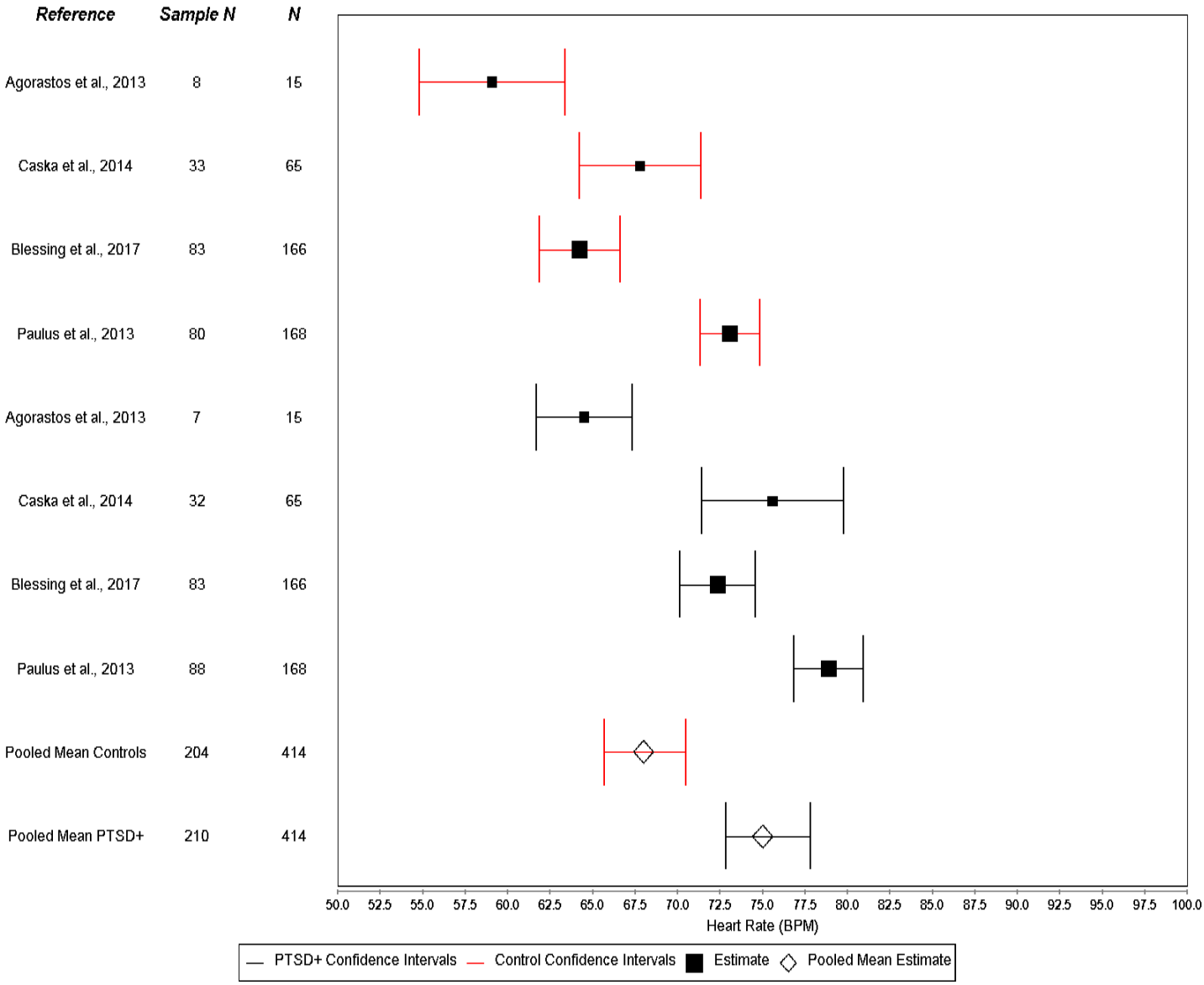
Cardiac Haemodynamics: Heart rate variability

Heart rate was reported in four articles (196, 205, 207, 208). Two articles used multivariable analysis (196, 205). One article reported a significant association between PTSD and elevated HR during the daytime (196) and one article did not, though it did report a significant association between PTSD and elevated HR at night-time (205).

The pooled mean estimate of heart rate was 68bpm for controls and 75bpm for PTSD samples (

Chapter 1 Figure **6**). The pooled SMD between PTSD and controls was .71 (95% Confidence Interval (CI) .51, .91) indicating a large positive effect size of PTSD on heart rate, thereby suggesting an increase in heart rate for those with PTSD compared to those without.

CHAPTER 1 FIGURE 6: MEAN AND POOLED MEAN HEART RATE ESTIMATES AMONG PTSD+ AND CONTROL EX-/SERVING PERSONNEL



Other facets of HRV were reported within five articles (195, 202, 205, 209, 214). One article used multivariable analysis to investigate the association between PTSD and a ratio of Low Frequency (LF) and High Frequency (HF) heart beats ((205)). LF/HF ratios refer to number of heart beats in the absolute power range of 0.04-0.15Hz (LF) and 0.15-0.4Hz (HF) and is a representation of both the amplitude (strength) and frequency of heart beats over time (216). Agorastos et al. (2013; (205)) found a significant association between PTSD and decreased intervals between normal to normal heart beats, lower LF/HF ratios at night and blunted differences between daytime and night time readings compared to controls (supplementary material 4).

Inflammatory markers

C-Reactive Protein (CRP), IF-γ, Interleukin-1 (IL-1), IL-1β, IL-6, Interleukin-10 (IL-10),TNF-α and pro-inflammatory cytokine scores were investigated in articles included in this review (196-198, 212); (

Chapter 1 Table 3). Pro-inflammatory cytokine scores consisted of standardised z-scores of IL-6, IL-1β, TNF-α, IF-γ and CRP integrated into a single variable (197, 198).

IL-10 was investigated in three articles (197, 198, 212). Two articles used multivariable analysis (197, 198). No significant associations were reported between IL-10 and PTSD.

Two articles investigated a pro-inflammatory cytokine score'. Both articles found significant elevated rates of pro-inflammatory cytokines within their PTSD+ samples compared to control samples (Chapter 1 Supplementary Materials 4).

Lipoproteins

High-Density Lipoproteins (HDL), cholesterol and triglycerides, as well as dyslipidaemia and hyperlipidaemia, were investigated in three articles included in this review, and all three used multivariable analysis (196, 201, 203) (

Chapter 1 Table 3). Significant associations between PTSD and elevated triglyceride levels (196) and elevated rates of dyslipidaemia/ hyperlipidaemia were reported (201, 203).

Tobacco use

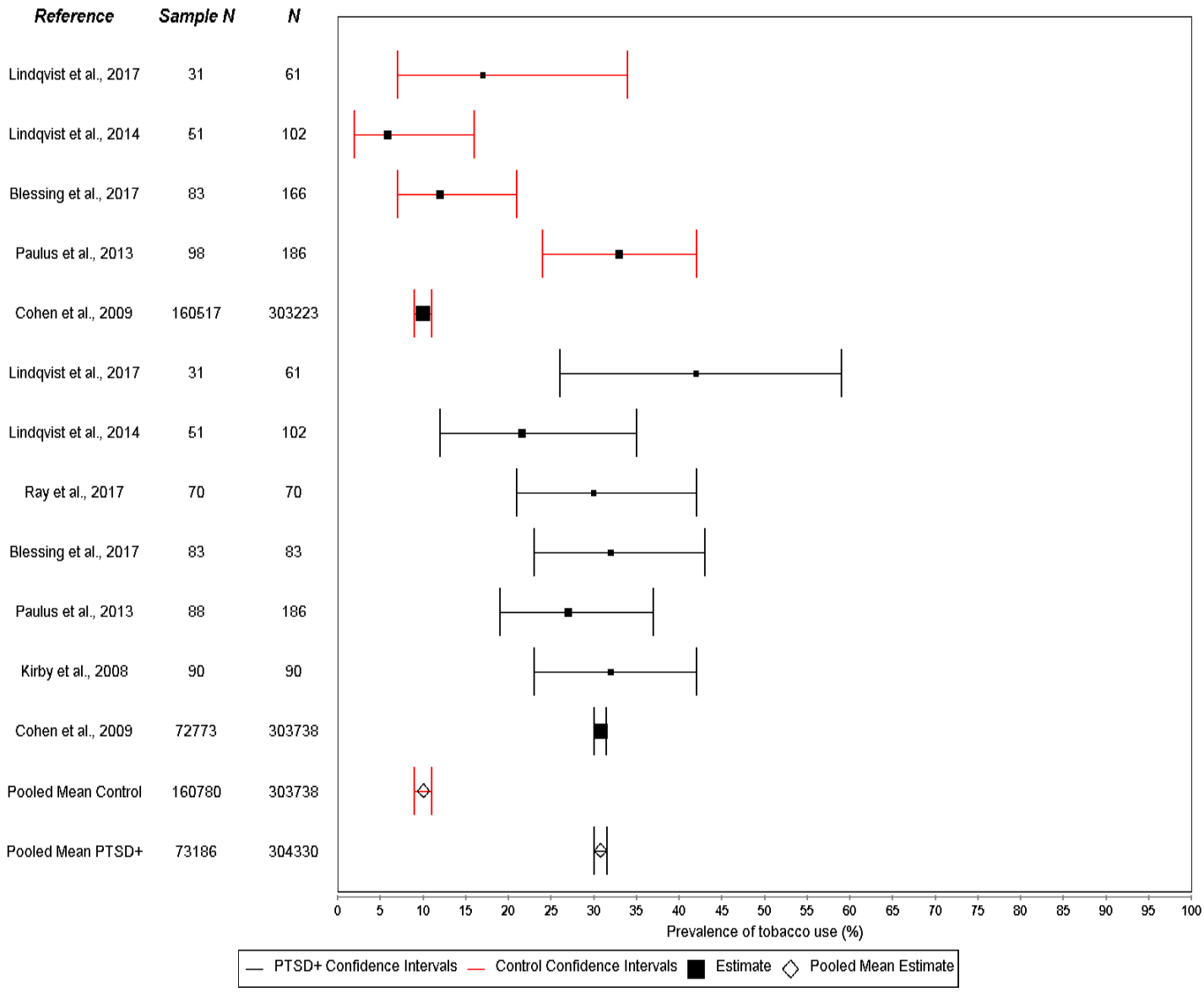
Eight articles reported on tobacco use or smoking behaviours (196-198, 200, 201, 207, 211, 214) (

Chapter 1 Table 3). Only one article used multivariable analysis (201), which found that PTSD was associated with tobacco use (Chapter 1 Supplementary Materials 4).

Estimates of tobacco use can be found in

Chapter 1 Figure 7. Pooled mean prevalence of tobacco use was 10% for controls and 30% for PTSD samples. The pooled RR of PTSD on use of tobacco was 2.21 (95% CI 1.16, 4.20).

CHAPTER 1 FIGURE 7: PREVALENCE RATES OF TOBACCO USE AMONG PTSD+ AND CONTROL EX-/SERVING PERSONNEL



Weight/Obesity

Eight articles reported on BMI or overweight/obese status (196-198, 203-206, 215) (

Chapter 1 Table 3). Three articles used multivariable analysis, and all three found a positive association between PTSD and higher BMI or overweight/obese status (203, 204, 215)).

CVD outcomes

Circulatory disease

Circulatory diseases include: hypertensive diseases; ischaemic heart diseases; pulmonary heart/circulation diseases; cerebrovascular diseases; diseases of arteries; arterioles and capillaries; diseases of veins, lymphatic vessels and lymph nodes and other form of heart disease or circulatory diseases. Two articles reported on circulatory diseases (203, 204) (Chapter 1 Table 4). Multivariable analysis was used in both articles, and both found a significantly higher prevalence of circulatory diseases in PTSD+ samples.

Other CVD

One paper investigated a large selection of CVDs (203) (Chapter 1 Table 4). Significant multivariable associations of note include a positive association between PTSD and elevated rates of acute myocardial infarction, pulmonary heart disease and atherosclerosis.

Methodological moderators

PTSD status

PTSD status was predominantly established using the Clinician Administered PTSD Scale (CAPS) (196-198, 200, 202, 205, 209, 210, 214). Diagnostic codes from the ICD-9 (201, 203, 204, 206, 213, 215), questionnaire scores (Posttraumatic Stress Disorder Checklist) (211) and a small amount of other, non-reported methods were also used (195, 207). Length of experienced PTSD was measured by time since trauma in one article (210). Four articles reported on a minimum length of time in their samples since diagnosis for a participant to be categorised as having PTSD, ranging from at least one month to one year (197, 198, 203, 213) (Chapter 1 Supplementary Materials 3).

Physical health status and technical details

CVD was typically established through ICD-9 classifications found in medical records. Blood pressure and other facets of heart function, when reported, were primarily established by ECG or other blood pressure monitors (Chapter 1 Supplementary Materials 3). Few articles

reported on technical details such as posture, time of day, caffeine use/restriction, fasting status etc.

Comparison samples

Comparison samples primarily consisted of combat-exposed veterans without PTSD. Recruitment populations were predominantly from clinical populations, such as veterans with other physical health/mental health conditions, e.g. attending the Veterans Health Administration for non-PTSD health problems (Chapter 1 Table 2).

Age

Age is significant when considering HPA functioning, as younger men have been found to elicit a higher hypothalamic drive (healthier cardiovascular functioning) in comparison to older men (217). Of the studies that reported a mean age for both PTSD+ and control samples (195, 196, 202, 205-208, 210, 212, 214), pooled mean age was 30.89 for PTSD+ and 32.70 for controls, indicating that the population included in this review is still relatively young.

Tobacco use

Tobacco use was usually presented as 'smoker' or 'non-smoker' (197, 198, 201, 207, 214), though little information was available with regards to frequency of smoking, lifetime smoking and definitions of being a smoker. Blessing et al. (2017; (196)) distinguished between smokers who used tobacco 'every day' and 'some days'. Kirby et al. (2008; (200)) reported that of their PTSD+ current smoker sample (n=29), 50% were heavy smokers (≥20 cigarettes a day).

Discussion

This systematic review reports that in those who deployed to Iraq or Afghanistan, PTSD is positively associated with an increased risk of CVD and several of its associated risk factors including elevated heart rate, obesity, tobacco use and dyslipidaemia. Not enough evidence was available regarding inflammatory markers or heart rate variability.

Blood pressure and heart function

Armed Forces ex-/serving personnel with PTSD appear to report elevated blood pressure (also represented in a diagnosis of hypertension). It is important to note that many of the participant samples included in this review had a low mean age (mean age range 24-34 years old). The Framingham study, a longitudinal cohort study investigating CVD in US adults, reported an increase of SBP with age, and that higher SBP represented higher peripheral

vascular resistance, a major proponent of coronary heart disease (218). Physical exercise is a major protective factor against the development of hypertension (219) and was not controlled for in any of the studies included in this review. Physical exercise is a major component of armed forces serving personnel lifestyle that might be responsible for the observed weight changes after discharge from the military (220). Blood pressure has been found to be higher in supine position when compared to sitting (221, 222), though the majority of studies included in this review did not report on posture during BP measurement.

Heart rate was found to be higher in PTSD samples compared to control samples (196, 205, 207, 208)). Higher heart rate is an independent risk factor of CVD (223). The relationship between higher heart rate and PTSD is established in both civilian and military populations (224) and could be mediated by the abnormal autonomic arousal associated with PTSD, as seen by the diminished tonic parasympathetic activity reported in Agorastos (2013; (205)). This might explain the higher prevalence of heart disease in PTSD populations (155). Smoking (189) and obesity (225) are both associated with elevated heart rates, so it is likely a combination of behavioural and biological mechanisms are responsible for the elevated heart rate seen in persons with PTSD.

Lipids and dyslipidaemia

Dyslipidaemia (including hyperlipidaemia) was positively associated with PTSD in the large cohort studies that investigated it ((201, 203). Dyslipidaemia is a risk factor for myocardial infarction (226). Blood lipids have been found to be directly correlated with diet (227), which was not controlled for in any studies included in this review. US Iraq/Afghanistan veterans with PTSD/depression have been shown to be at risk for binge-eating (228), the impact of which could partially explain some of the lipid profiles seen in this review, as well as the higher rates of obesity.

Inflammatory markers

A chronic inflammatory process is known to be associated with coronary heart disease, especially atherosclerosis, in which the arterial walls are damaged by chronic inflammatory responses (176-179). Passos et al. (2015; (180)) reported higher concentrations of IL-6, IL-1β, TNFα and IF-γ in those that report symptoms of PTSD. In contrast, this review found mixed evidence for elevation of these markers (196-198, 212). Whilst evidence of any single inflammatory marker was mixed, both Lindqvist et al. studies (2014, 2017; (197, 198)) did find a trend for elevated pro-inflammatory cytokines in their PTSD+ samples. The

differences in individual inflammatory cytokines reported between articles suggests a complex interplay of cytokine concentrations that may change depending on severity or regularity of the acute phase response/stress response in those with PTSD. This review only included baseline levels of inflammatory markers (e.g. inflammatory markers found in the blood not during/in response to a stress task), which might explain why no consistent differences between PTSD+ and controls were found.

Moderators

Potential moderators in the review include methodology involved in measurement, comparison samples, and PTSD symptomology. Articles recruiting from clinical centres usually required the participants to attend multiple appointments within a one- or two-year period, which implies comparison groups may represent non-healthy populations. This may be particularly important when looking at outcomes/risk factors like HRV, which is reported to be low in many physical illnesses as well as mental illnesses (135, 170, 229). Traumatic physical injuries (e.g. amputations) also represent a unique impact on elevated risk for CVD (230) which was not controlled for in any article included in this review.

Little information was available on length of time study participants had experienced PTSD. This is an important area to investigate, as it is unknown how long it takes for the biological impact of PTSD to be reflected in e.g. blood pressure, heart rate etc. PTSD symptom severity might also affect these areas and should be explored in future research.

Strengths and Limitations

This review is the first to combine non-diagnostic laboratory results of cardiovascular risk factors and CVD in military Iraq/Afghanistan ex-/serving personnel, including a range of heart function and inflammatory markers. The review searched a large number of databases, used PRISMA guidelines and had two authors review the quality of papers using validated methods (194).

Tobacco use was reported in a suitable amount of papers to construct a forest plot and estimate a RR, however many papers did not report amount of tobacco use (e.g. amount of cigarettes smoked per day). Similarly for heart rate, whilst only daytime examinations were used to generate forest plots, posture (e.g. standing, sitting or supine) was not accounted for. Both of these limitations should be accounted for when interpreting the forest plots included in this review.

This review focussed on what was deemed a suitable range of clinical indicators of CVD, though this was not all inclusive. Other indicators, such as alcohol abuse, substance abuse and comorbid mental health disorders, were not included despite being known risk factors for CVD (231-233) and are also associated with PTSD (105, 108). Some studies included in this review excluded or controlled for comorbid depression/axis 1 mental health disorders (supplementary material 4). Few studies were longitudinal in nature, and all studies were completed on US veterans, thus results of this review need to be interpreted with caution.

Future research

Future research should standardise aspects of research such as time of day, posture, tobacco use, caffeine use, and fasting due to their impact on cardiovascular function, and it is suggested a DELPHI panel might make recommendations which elements of methodology should be standardised across investigations into HRV, inflammation and other cardiovascular risk factors (234). Investigations of PTSD symptom severity and length of time PTSD is experienced before cardiovascular risk factors/disease presents are required. Good quality, methodologically sound studies are still needed to explore the mechanisms between PTSD and CVD in military populations.

Conclusions

The results of this review suggest that military ex-/serving personnel with PTSD are at increased risk of CVD through a series of both behavioural and biological mechanisms. Furthermore, these risks/outcomes are being shown in a relatively young demographic of men, whose risk of CVD/risk factors should be relatively low (235). This is important to note for clinicians working with military ex-/serving personnel, who might benefit from considering regular monitoring/health advice regarding hypertension, smoking status, lipid profiles and weight.

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Conflict of interest: None

Key Messages

- Compared to previous military operations, UK Armed Forces personnel were exposed to more explosive/blast injuries, mostly from improvised explosive devices.
- UK Armed Forces personnel who deployed to Afghanistan were more likely to survive more severe combat injuries compared to personnel who sustained injuries on any previous deployment.
- Evidence suggests that those who experienced amputation injuries have reductions in quality of life, poorer mental health and wide-ranging physical health consequences, though the specific long-term outcomes for those who sustained amputations as a result of injury in Afghanistan are largely unknown.
- Evidence for those who experienced non-amputation injuries varies substantially depending on the type of injury sustained, though are thought to include reductions in quality of life, poorer mental health and wide-ranging physical health consequences. Similarly, the specific long-term outcomes for those who sustained these types of injuries as a result of deployment to Afghanistan are largely unknown.
- Mental health consequences of military deployment to Afghanistan depend on occupational role and combat experiences. UK Armed Forces personnel who deployed in a combat role and have left service are at greater risk of reporting poor mental health outcomes including CMD and PTSD compared to those who deployed in non-combat roles and also left service.
- Mental illness is not the only mental health consequence of military deployment to Afghanistan. Psychological thriving, including PTG, is a possible outcome.
- Mental illness has been shown the be associated with worse cardiovascular functioning and increased rates of CVD. Military personnel who deployed to Afghanistan and experienced PTSD were more likely to report worse cardiovascular risk profiles and subsequent CVD compared to those who deployed and did not experience PTSD. These profiles were evident despite the fact these individuals were still relatively young at assessment.
- Investigation into the association between PTG and cardiovascular functioning is limited but suggests that PTG is associated with better cardiovascular functioning.

Hypotheses/aims

This thesis will examine both mental illness and PTG outcomes that occur in those who sustained a combat injury during deployment to Afghanistan and compare these outcomes to a similar uninjured group. This thesis will also explore the cardiovascular risk factors of UK Armed Forces personnel with PTSD symptoms, assessing whether PTSD symptoms are associated with a poorer cardiovascular risk profile and which symptom clusters best explain these associations. Similarly, this thesis will explore the cardiovascular risk profile of those who exhibit PTG, assessing which factors of PTG best explain these associations.

Aim 1.1 Compare the rates of PTSD, depression, anxiety and mental health multimorbidity between injured and uninjured groups of Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).
Aim 1.2 Investigate whether subgroups of the injured group, specifically those who sustained an amputation injury and non-amputation injury, exhibit differences in rates of these outcomes.

Aim 2.1 Investigate PTG experienced as a result of deployment to Iraq/Afghanistan between injured and uninjured groups of Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).
Aim 2.2 Investigate whether subgroups of the injured group, specifically those who sustained an amputation injury and non-amputation injury, exhibit differences in rates of deployment related PTG.
Aim 2.3 Investigate whether depression, PTSD and pain mediate the relationship between combat injury and PTG.

Aim 3.1 Examine whether PTSD symptom clusters are associated with cardiovascular risk factors including inflammation, cardiometabolic effects and haemodynamic functioning in a cohort of injured/uninjured Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).
Aim 3.2 Assess the relative importance of these symptom clusters via variable selection procedures and confirm results via robust regression modelling.

Aim 4.1 Examine whether factors of PTG will be associated with better cardiovascular health indicators including inflammation, cardiometabolic effects and haemodynamic functioning in a cohort of injured/uninjured Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).

Aim 4.2 Assess the relative importance of the factors of PTG in these associations via variable selection procedures and confirm results via robust regression modelling.

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Methodology:
ArmeD SerVices TrAuma and RehabilitatioN OutComE study

"Providing high quality evidence that will ADVANCE future healthcare policy surrounding physically combat injured and major trauma patients"

Overview

In this chapter I will describe the methodology employed by the ADVANCE cohort study, including the ADVANCE study protocol. This includes details on the cohort participant selection of injured personnel and the frequency matching employed to create the uninjured comparison group, as well as the measurement tools employed to assess the physical and psychological health of the cohort. The section will also include details specific to the IMPACTS study, including ethics application, data collection procedure and data analysis.

ADVANCE cohort study protocol

This is the Author's Accepted Manuscript version of the article: "A Study Protocol for a Prospective, Longitudinal Cohort Study Investigating the Medical and Psychosocial Outcomes of United Kingdom Combat Casualties from the Afghanistan War: the ADVANCE Study" accepted for publication in 'BMJ Open' on 21/09/2020. To view the published version, please visit: http://dx.doi.org/10.1136/bmjopen-2020-037850

A Study Protocol for a Prospective, Longitudinal Cohort Study Investigating the Medical and Psychosocial Outcomes of United Kingdom Combat Casualties from the Afghanistan War: the ADVANCE Study

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Abstract:

Introduction

The Afghanistan war (2003-2014) was a unique period in military medicine. Many service personnel survived injuries of a severity that would have been fatal at any other time in history; the long-term health outcomes of such injuries are unknown. The **A**rme**D** Ser**V**ices Tr**A**uma and Rehabilitatio**N** Out**C**om**E** (ADVANCE) study aims to determine the long-term effects on both medical and psychosocial health of servicemen surviving this severe combat related trauma.

Methods and analysis

ADVANCE is a prospective cohort study. 1200 Afghanistan-deployed male UK military personnel and veterans will be recruited and will be studied at 0, 3, 6, 10, 15 and 20 years. Half are personnel who sustained combat trauma; a comparison group of the same size has been frequency-matched based on deployment to Afghanistan, age, sex, service, rank and role. Participants undergo a series of physical health tests and questionnaires through which information is collected on cardiovascular disease (CVD), CVD risk factors, musculoskeletal disease, mental health, functional and social outcomes, quality of life, employment, and mortality.

Ethics and dissemination

The ADVANCE Study has approval from the Ministry of Defence Research Ethics Committee (MODREC; protocol No:357/PPE/12) agreed 15th January 2013. Its results will be disseminated through manuscripts in clinical/academic journals and presentations at professional conferences, and through participant and stakeholder communications.

Registration

The ADVANCE Study is registered at ISRCTN ID: ISRCTN57285353.

Article Summary: strengths and limitations of this study:

- ADVANCE is, worldwide, the only longitudinal cohort study to evaluate the effect of combat trauma on a range of health indicators in military personnel who served in the Afghanistan war.

  - ADVANCE will provide a wide range of longitudinal data across sociodemographic, physical health and mental health outcomes, providing evidence for incidence and risk of disease and other non-disease related outcomes.
  - ADVANCE will provide high levels of evidence that will influence future healthcare of combat and major trauma patients.
  - Participants were injured between five to 16 years prior to baseline data collection, and the length of time since injury may have an effect on various physical and mental health indicators.
- As with any cohort study, there is potential for response bias.

Introduction

During the Afghanistan war between 2003 and 2014, the UK military sustained over 2400 combat casualties [1]. Many had such severe injuries that in previous conflicts they would have died, if it were not for the trauma care provided by the UK Defence Medical Services (DMS); they are frequently termed 'unexpected survivors' [2]. Rehabilitation took place at the Defence Medical Rehabilitation Centre at Headley Court, often over many months, and the short-term outcomes have been favourable [3-8]. However, the longer-term outcomes of this cohort of severely injured personnel are unclear. Understanding medical and psychosocial outcomes in this population will provide evidence for, and influence the future care of, patients in trauma and rehabilitation services worldwide.

Previous studies into war veterans from earlier conflicts, such as the Vietnam war and World War II, have investigated long-term health outcomes. However, studies investigating combat injury and consequent adverse cardiovascular disease (CVD) outcomes [9-36] have low strength of evidence for cause and effect. Others have investigated only mental health outcomes [37-39] or mortality [23, 38-44]. Studies of musculoskeletal (MSK) outcomes in combat amputees, such as osteoarthritis/osteopenia, pain and physical functioning, have been either retrospective, small in numbers, inconclusive [45-47], short-term [48], or focussed on surrogates of outcome such as return to military duty [49]. Many studies investigating veterans' long-term outcomes are either not specifically related to combat trauma [22-37] or are of cross sectional or retrospective design making it difficult to draw robust conclusions from them [10-13, 15-25, 27, 29, 30, 32, 34, 38, 39].

Current Knowledge

Cardiovascular Disease

Combat injuries have been shown to be associated with CVD in Finnish war veterans [14], Israeli lower-limb amputee veterans [18] and US Vietnam veterans [50]. Whilst this evidence suggests battlefield-injured ex- or serving personnel are at higher risk of CVD, the strength of evidence is low [14, 18, 50], and the only UK data [36] challenges the findings, suggesting that veterans may be at lower risk for acute myocardial infarction. Furthermore, the mechanisms that drive this potentially increased risk are poorly understood.

Systolic blood pressure and hypertension, diabetes mellitus, High sensitivity C-Reactive Protein (HsCRP), lipid profiles (e.g. cholesterol, triglycerides etc.), heart rate, obesity, and smoking are well validated measures of CVD risk [51]. Large artery stiffness, leading to

increased pulse wave velocity (PWV) and accelerated arterial wave reflections causing an increase in myocardial demand, central systolic blood pressure and a decrease in coronary artery perfusion pressure, are promising additional risk markers. Increased PWV has been shown to be an independent predictor of cardiovascular morbidity and mortality in several population groups, including healthy controls [52-57], and has the potential to identify CVD risk earlier than traditional risk factors and to help better understand the aetiology of CVD.

Heart Rate Variability (HRV) is another risk factor for disease. Temporal changes in cardiac beat-to-beat intervals are subject to continuous autonomic nervous system influence and competing sympathetic versus parasympathetic control. As a marker for altered autonomic balance, HRV has been linked to adverse clinical conditions such as cardiac death, stroke and poor mental health [58-64].

In a recent systematic review and meta-analysis [9] it was concluded that there is currently insufficient evidence to confidently link combat related traumatic injury to an increased risk of CVD and associated risk factors. The review identified the need for high quality data from a more contemporary and prospective study.

Musculoskeletal Health

The consequences of severe musculoskeletal (MSK) trauma often result in functional limitations to the individual, and a significant socioeconomic cost to society [65]. An improved understanding of the effect of trauma and amputation on the musculoskeletal system, and of disease processes and progress over time, is essential to provide effective long-term care of complex trauma casualties. There is some evidence to suggest an association between osteoarthritis and amputation [45, 64], possibly reflecting alterations in the biomechanics of the amputee's movement, by which degenerative changes such as osteoarthritis of the knee/hip can occur [66, 67]. However, few risk factors have been identified regarding hip/knee osteoarthritis [47]. Similarly, femoral neck osteopenia [45, 46, 68] and back pain [69, 70] appear to be prevalent in traumatic amputee populations. Long term longitudinal prospective evidence of disease prevalence, risk and progression is required to understand the aetiology of these diseases.

Mental Health

Amongst UK military personnel and veterans who deployed to the Iraq and Afghanistan wars, the prevalence of common mental disorders is estimated to be 22% [71]. For veterans with physical impairments, reported rates of common mental disorders range from 10-46%

for depression and 16-36% for anxiety disorders (excluding PTSD) [72]. However, these figures come from a predominantly US population and have not been specifically investigated in combat injured populations.

The prevalence of PTSD in UK military veterans who served during the Iraq/Afghanistan conflicts has increased, from 4% in 2006 [73] and 2010 [37] to around 6% in 2018 [71]. This, along with reported rates of PTSD ranging from 2-59% in ex-/serving personnel with a physical impairment [72], highlights the need to be monitoring mental health in military personnel and especially in those who are combat casualties.

The incidence of other important long-term outcomes including all-cause mortality, hearing loss, drug and alcohol use, physical function, quality of life, social and employment outcomes are largely unknown, particularly in combat casualties.

Hypotheses & Objectives

The objective of the **A**rme**D** Ser**V**ices Tr**A**uma Rehabilitatio**N** Out**C**om**E** (ADVANCE) study is to investigate the long-term medical and psychosocial outcomes of UK military personnel who sustained combat trauma. We hypothesise that combat trauma casualties will have an increased incidence of adverse medical, psychosocial and vocational long-term outcomes compared to equivalent but non-injured service personnel.

Methods and Analysis

Study design

The ADVANCE Study is a prospective 20-year cohort study. The ADVANCE study aims to recruit 'exposed' adult males (*n*=600) who sustained physical combat trauma while on deployment in Afghanistan and required aeromedical evacuation to a UK hospital. A frequency matched unexposed comparison group (*n*=600) of males without combat-injury is also recruited.

Study Population

Participants are recruited from ex-/serving UK military personnel who deployed on combat operations to Afghanistan between 2003 and 2014.

Recruitment

Recruitment started in March 2016 and will be finished by Autumn 2020; the inclusion and exclusion criteria are listed in

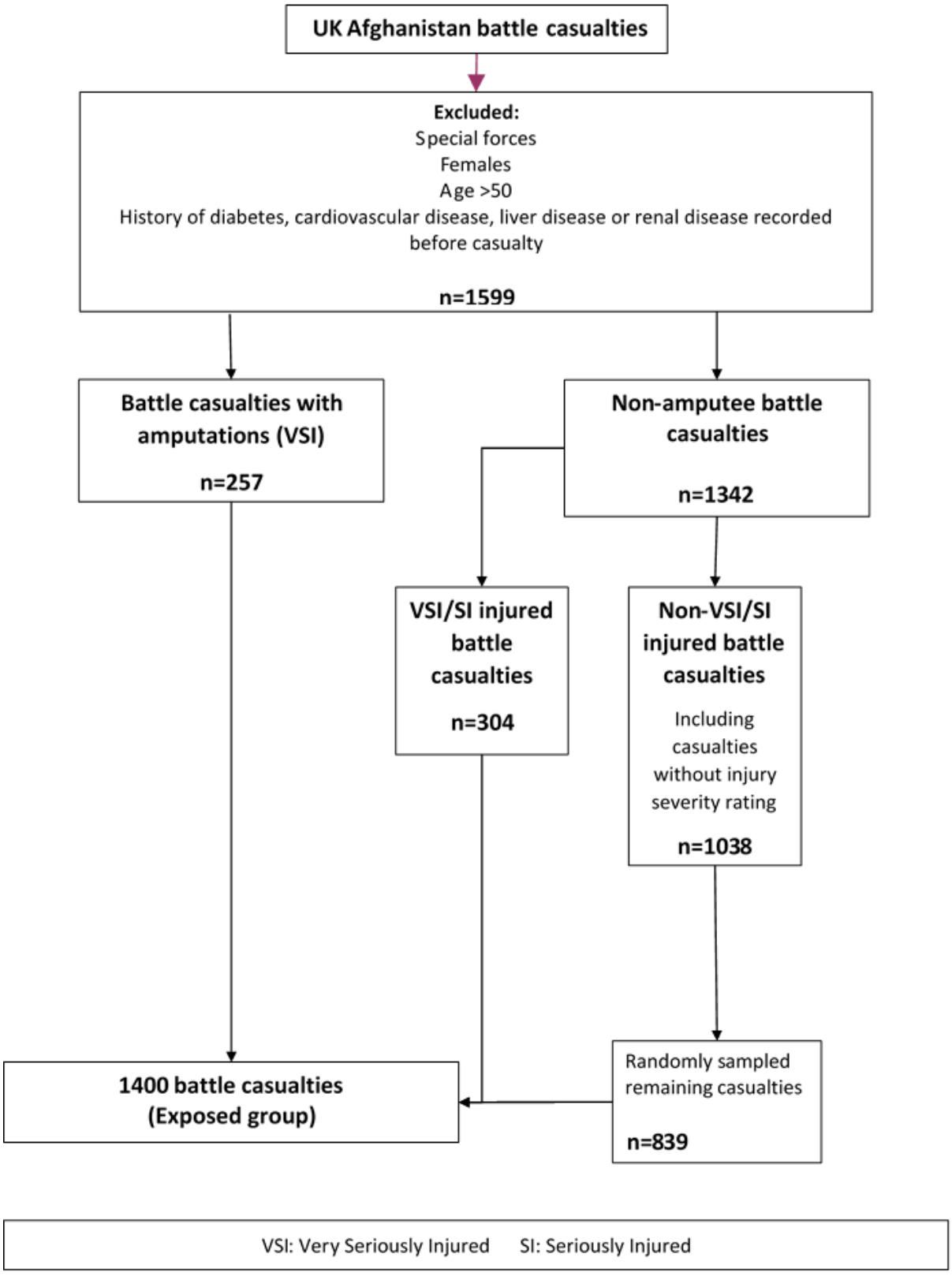
Chapter 2 Table 1.Volunteers from both the "exposed" and "comparison" cohorts are recruited from two lists provided by Defence Statistics UK. The first is a list of serving and ex-serving military personnel who sustained a combat injury (*n*=1400). The second is a list of men who had not sustained an injury for the comparison group(*n*=2100), frequency matched to the injured group based on age, service, rank, role, regiment and deployment (Figures 1 and 2). Deployment refers to a specific deployment period of interest. For the exposed (injured) group, this is the deployment period in which they sustained their injury. The unexposed (comparison) group were frequency matched based on deploying within the same period without sustaining a physical combat related injury. The following data sources were used to identify the potential participants: the initial Notification of Casualty System (NOTICAS); the Defence Patient Tracking System; the Defence Medical Information Capability Programme (DMICP); the Defence Medical Rehabilitation Centre (DMRC) Complex Trauma Database; the DRMC Prosthetic database; the Joint Theatre Trauma Registry; and the Joint Personnel Administration (JPA).

Participants are recruited through postal mailouts, e-mail invitations and telephone calls, and where necessary traced via JPA contacts, if still serving, and through electoral roll data, social media or advertising via military charities.

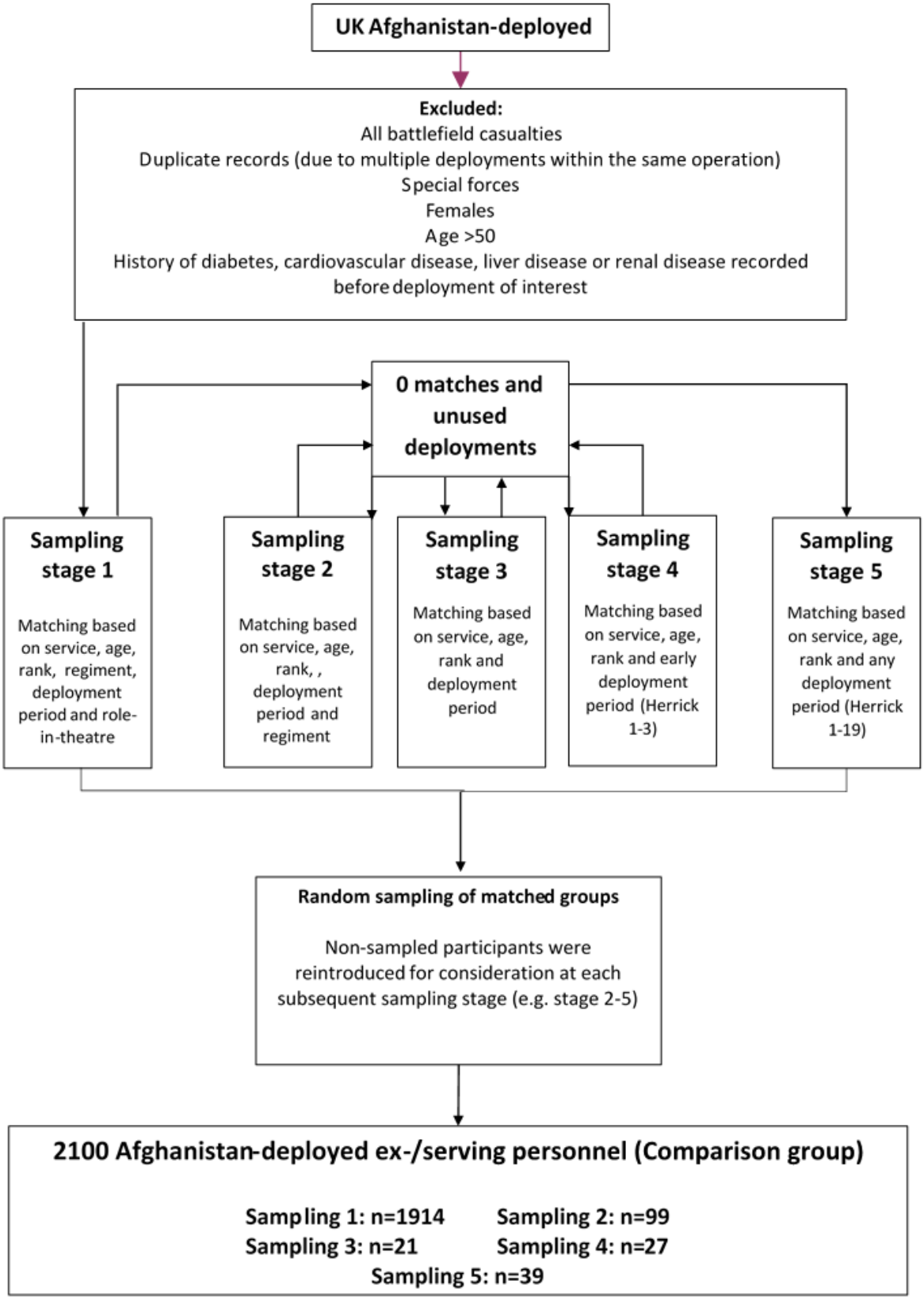
CHAPTER 2 TABLE 1: INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria
• UK Armed services personnel
• Male
• Exposed only: Sustaining physical battlefield trauma, while on deployment to Afghanistan, requiring aeromedical evacuation and direct UK hospital admission
• Exposed only: Injured between 2003 and the end of 2014.
Exclusion Criteria
➢ Females
➢ Patients who are unwilling or unable to give informed consent
➢ Patients with established CVD (previous stroke or transient ischaemic attack [TIA], ischaemic heart disease [IHD], peripheral vascular disease) prior to injury/deployment of interest
➢ Past medical history of diabetes prior to injury/deployment of interest
➢ Past medical history of renal or liver disease prior to injury/deployment of injury
➢ Aged <18 and >50 years
➢ Active acute infection with at least 2 systemic features of sepsis*, at the time of recruitment, as defined below. Potential participant with active acute infection will be considered for recruitment once the acute illness is treated and resolved. • Temperature >38ºC or <36ºC • Heart rate>90beats/min • Respiratory rate >20 breaths/min *participants suffering from an acute infection will be excluded initially but will be re-approached to take part once the infection resolves.*
➢ Comparison group only: subsequent combat injury sustained whilst on deployment in Afghanistan after matching.
➢ *American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. 1992

CHAPTER 2 FIGURE 1: SAMPLING FLOWCHART FOR INJURED PERSONNEL



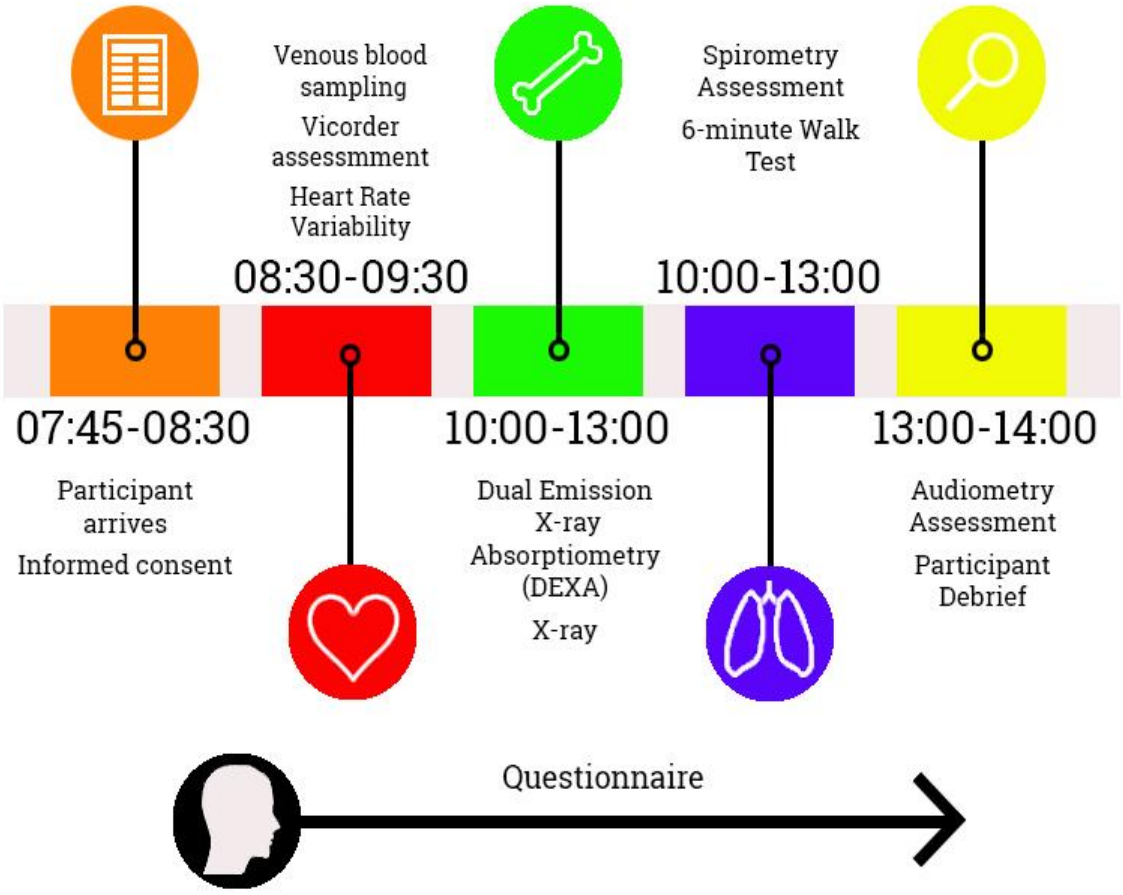
CHAPTER 2 FIGURE 2: SAMPLING FLOWCHART FOR COMPARISON PERSONNEL



Setting

Data is collected during a one-day study visit to the Defence Medical Rehabilitation Centre at Headley Court (March 2016-August 2018) or Stanford Hall (after August 2018). The study day starts at 07:45, and participants arrive in a fasted state (eight hours); investigations are completed by 14:00 (Figure 3). Participants will be invited to attend follow-up at 3, 6, 10, 15 and 20 years. Informed written consent is obtained from the participants by trained research personnel. This includes consent for access to central NHS and Ministry of Defence (MoD) medical records and for required data linkages to be conducted.

CHAPTER 2 FIGURE 3: TIMELINE OF ADVANCE STUDY DAY



Outcome and Confounder Variables

Core outcome variables collected at baseline are detailed below. These may expand throughout the 20-year duration of the study.

Cardiovascular Disease

Participants are assessed for onset of CVD at each visit, determined by the onset of individual components of the Major Adverse Cardiovascular Endpoint (MACE), a composite of cardiovascular death, non-fatal myocardial infarction, stroke, transient ischemic attack, arterial revascularisation (coronary artery bypass grafting, percutaneous coronary intervention, carotid endarterectomy or stenting and peripheral arterial stenting or bypass) and the onset of peripheral vascular disease, angina or hypertension.

This combined cardiovascular endpoint is internationally recognized and validated in cardiovascular outcome research [74-81]. Each participant will be flagged with the National Health Service Central Register (NHSCR) to provide date and cause of death.

Cardiovascular Risk

BIOMETRIC ASSESSMENT

Height is measured using a stadiometer (SECA 704, UK); for men with bilateral leg amputations, reported pre-injury height will be taken from medical records. Weight is measured using electronic scales (SECA 956, UK). Abdominal waist and hip circumference are measured manually using a tape measure. BMI is calculated using an adjusted formula for amputees (Tzamaloukas et al., 1994).

VICORDER ASSESSMENT

The Vicorder (Skidmore Medical Limited, Bristol, United Kingdom) is a validated device that measures arterial PWV and complex Pulse Waveform Analysis (PWA) [82-84]. PWV is quantified by the simultaneous recording of arterial pulse waveforms at the carotid and femoral arteries using an integrated neck transducer and upper thigh cuff respectively [83]. Using the PWA, the Vicorder also provides a non-invasive measure of peripheral and central blood pressure and arterial central and peripheral augmentation index (AI) [82]. Its measurement of PWV has been shown to have a within-subject coefficient of variation of 2.8% [84]. The central and peripheral measurements of arterial stiffness have been shown to be independent predictors of CVD risk [85].

The assessment takes place on a hospital bed at a 30-degree angle in the supine position, in a room that is temperature and noise regulated. Three measures of PWA are conducted using the upper left arm cuff. This cuff is then removed, and a neck transducer is used along with a

cuff on the upper left thigh to conduct three measures of pulse wave velocity. All tests are completed ipsilaterally unless this is impossible due to amputation, in which case assessments are completed contralaterally. Diastolic and systolic blood pressure are also taken in the supine position using the Vicorder device with a cuff attached to the upper left arm.

HEART RATE VARIABILITY (HRV)

Cardiac interbeat intervals for the measurement of HRV is undertaken using an electro-cardiogram (ECG) device (Mega Motion Faros 180 recorder; Mega, Finland). Two consecutive 5-minute recordings of ECG-derived cardiac interbeat intervals will be obtained using spontaneous breathing followed by a 5-minute paced breathing exercise, both in a supine position [86] [87]. Tests are completed in a noise and temperature-controlled environment. Measures of HRV are undertaken offline using the recorded cardiac inter-beat data.

SERUM SAMPLES

Venous blood is drawn and analysed for full blood count, lipids, glucose, liver function, urea and electrolytes, HbA1c and HsCRP (Supplementary materials 1).

QRISK

10-year cardiovascular risk will be determined using the QRISK calculator [88] with biometric, sociodemographic and clinical data.

RESPIRATORY FUNCTION

The participant's respiratory function is measured using a PC Spirometer (Trueflow, NDD, Switzerland) to assess basic respiratory capability and its contribution to functional capacity. A forced expiratory test, without noseclips, is completed with the participant sitting upright. Three acceptable readings are sought, with a maximum of eight attempts made.

Traumatic/Mild-Traumatic Brain Injury (TBI/mTBI)

TBI/mTBI occurrence is assessed using a clinician administered interview [89] and post-concussive symptoms are assessed using Participant Reported Outcome Measures (PROMS) [90] (Chapter 2 Table 2).

CHAPTER 2 TABLE 2: PATIENT REPORTED OUTCOME MEASURES: MUSCULOSKELETAL, PAIN AND PHYSICAL FUNCTION

	MEASURE	QUESTIONNAIRE TYPE	N ITEMS
Musculoskeletal Disease			
Amputee Physical Functioning	Amputee Mobility Predictor Questionnaire/Assessment [103-105]	Clinician Assessment	24
	Prosthetic functioning	Self-report	6 (per missing limb)
	Prosthetic Socket Comfort Score [108]		
	Special Interest Group in Amputee Medicine (SIGAM) [134]	Clinician Assessment	12
Pain	Brief Pain Inventory-Short Form [114]	Self-report	15
	Disability Arm, Shoulder and Hand Questionnaire [109, 110]	Self-report	30
	DN4* [116]	Self-report	7
	Knee Osteoarthritis Outcomes Score [135, 136]	Self-report	42
	Manchester-Oxford Foot Questionnaire [113]	Self-report	16
	Neuropathic Pain Symptom Inventory [115]	Self-report	12
	Non-Arthritic Hip Score [112]	Self-report	20
	Oswestry Disability Index [111]	Self-report	10
	Pain Catastrophising Scale [117]	Self-report	13
Physical fitness	International Physical Activity Questionnaire [137]	Self-report	20

	MEASURE	QUESTIONNAIRE TYPE	N ITEMS
Mental Health			
Alcohol and Drug Use	Alcohol Use Disorder Identification Toolkit [121]	Self-report	10
	Drug Use Disorder Identification Toolkit [122]	Self-report	11
Common Mental Disorders	Generalised Anxiety Disorder-7 [123]	Self-report	7
	Patient Health Questionnaire-9 [124]	Self-report	9
Post-Traumatic Growth	Deployment-related Post-Traumatic Growth Inventory* [127]	Self-report	21
Post-Traumatic Stress Disorder	Post Traumatic Check List-Civilian [125]	Self-report	17
	Post Traumatic Check List-DSM V [126]	Self-report	20
Sleep	Insomnia Severity Index* [138, 139]	Self-report	4
	Pittsburgh Sleep Quality Index* [140]	Self-report	4
Other			
Adverse Childhood Experiences	King's Military Cohort: Health and Well-being Survey* [120]	Self-report	12
Mild-/Traumatic Brain Injury	Ohio-State University Traumatic Brain Injury Identification Method Questionnaire [89]	Clinician Interview	13
	Rivermead Post-Concussion Questionnaire [90]	Self-report	18
Quality of Life	Arizona Sexual Experiences Scale [129]	Self-report	5
	EQ-5D-5L [128]	Self-report	

	MEASURE	QUESTIONNAIRE TYPE	N ITEMS
Social Support	Multidimensional Perceived Social Support Questionnaire [130]	Self-report	12

**Adapted versions*

Musculoskeletal Disease

RADIOGRAPHIC ASSESSMENT FOR OSTEOARTHRITIS AND SACROILIITIS

Participants have radiographic assessment for osteoarthritis of the knees and hips and for chronic sacroiliitis. Posterior-anterior views with the knees in semi-flexed position (7-10 degrees) using the Synaflexer frame^{TM} are performed as per recommendations for the assessment of osteoarthritis [91-94]. Anterior-lateral and skyline views (inferior-superior) of the patellofemoral joint with the knees in 30 degrees of flexion are taken [94, 95]. Hips are also assessed radiographically with an AP pelvis film (focal length 100cm, hips internally rotated 15 degrees) [96]. Radiographs are scored according to the Kellgren and Lawrence radiographic osteoarthritis scoring method [97] for both the hip and the tibiofemoral joints of the knee. The patella femoral joint will be scored using the Osteoarthritis Research Society International (OARSI) scoring method [98]. AP pelvis x-rays will also be scored for sacroiliitis via the modified New York score [99].

DUAL EMISSION X-RAY ABSORPTIOMETRY (DEXA) ASSESSMENT FOR OSTEOPOROSIS AND BODY COMPOSITION

Total body composition, visceral fat, lean muscle mass and bone mineral density are recorded using body composition DEXA (Headley court: Vertec Horizon, UK; Stanford Hall: Vertec Discovery, UK) [100] which has previously been used in a military population [101, 102]. Scans of the whole body, right and left proximal femur and lumbar spine are performed. For the whole-body scan participants are laid in the supine position, with their head and spine aligned with the centre of the DEXA table with legs apart and feet turned in; participants remain in this position for approximately 10 minutes. For the right and left proximal femur, the relevant leg is abducted to allow the shaft of the femur to be parallel to the table, and the relevant foot strapped in. Participants remain in this position for seven minutes for each leg. For the lumbar spine, legs are elevated onto a square block and hips flexed at a 70-degree angle; participants remain in this position for seven minutes.

Physical Function and Pain

Physical function is assessed using a mixture of clinician administered tests, including the Amputee Mobility Predictor Questionnaire (AMP-Q), Special Interest Group in Amputee Medicine (SIGAM) mobility grades, the six-minute walk test, and PROMS (Chapter 2 Table 2).

The AMP-Q assesses an amputee's ability to complete physical tasks ranging from balance, reach, weight distribution/gait and walking [103-105], from which a SIGAM mobility

grading is assigned. The six-minute walk test evaluates functional capacity by measuring the distance an individual is able to walk over a total of six minutes on a hard, flat surface; it is valid in both the able-bodied and amputees [106, 107]. The goal is for the individual to walk as far as possible in six minutes at a self-directed pace with rest as needed as they traverse back and forth along a marked walkway.

PROMS used (Chapter 2 Table 2) assess prosthetic functioning, including socket comfort [108] and usage of prosthetics. Pain is assessed in specific areas of the body (shoulders, arm, hand [109, 110], back [111], hip [112], foot [113], phantom pain and overall pain [114]) as well as type of pain (e.g. neuropathic) [115, 116] and effects of pain (e.g. pain catastrophising) [117].

AXIAL SPONDYLOARTHRITIS

The presence of the gene HLA-B27, inflammatory back pain and the spondyloarthritis criteria [118, 119] are used to assess the prevalence of spondyloarthritis (axSpA). Inflammatory back pain is assessed using the ASAS experts' Inflammatory back pain criteria [119] and classification of axSpA through the Assessment of Spondyloarthritis International Society (ASAS) classification criteria [118].

MENTAL HEALTH

Mental health is assessed using PROMS (Chapter 2 Table 2) investigating adverse childhood events [120], alcohol and drug use [121, 122], common mental disorders [123, 124], PTSD [125, 126], post-traumatic growth [127], quality of life [128, 129] and social support [130].

Sociodemographic and Educational/Employment History and Outcomes

SOCIODEMOGRAPHIC

Sociodemographic information from time of injury/deployment including age, rank and regiment are provided by Defence Statistics. Other sociodemographic data (e.g. postcode, ethnicity etc.) will be collected at baseline and, where there may be changes, at all subsequent visits via questionnaire.

EMPLOYMENT OUTCOMES

Current and historic employment/education are recorded using an employment history questionnaire. Reasons for leaving the Armed Forces, highest level of educational attainment and veteran specific outcomes will be measured as per the King's Military Cohort: Health and Well-being Survey [71, 73, 131].

Bio-Sample storage and Other Serum Samples

Approximately 20mL of blood (whole blood/plasma/serum/DNA) and 50ml of urine are stored at -80^{o}C for assay of any future biomarkers of cardiovascular, MSK or other disease. Venous blood will also be assayed for a standard profile of male hormones including testosterone, follicular stimulating hormone (FSH), luteinising hormone (LH) and sex hormone binding globulin (SHBG) at each follow-up visit.

Audiology

Following simple otoscopic examination, an Amplivox CA850 4A audiometer with headphones is used to test hearing in a soundproofed booth. Both the audiometry and otoscopic examination follow recommended procedures from the British Society of Audiology [132].

Sample size

Sample size calculations (GraphPad StatMate version 2.00 for Windows (GraphPad Software) were based on the primary composite CVD endpoint. Published data have shown a greater risk of a CVD event (hazard ratio of $\geq$1.70) among those with traumatic injury compared to healthy controls [14, 18]. Given the age and demographic of the target population, event rates are likely to be low. However, the study is using a well-defined, published and measurable, broad composite CVD primary endpoint and has a prolonged follow-up period which both significantly reduce the sample size needed to maintain statistical power.

The rate of the primary MACE endpoint has been estimated using data from similarly aged populations [76, 79]. A primary composite CVD event rate of $\geq$10% at 20 years is expected in the comparison group with a hazard ratio of $\geq$1.7 in the combat trauma group. Based on this assumption we have calculated that a sample size of at least 400 in both the battlefield trauma exposed group and the non-exposed group would provide >80% power to detect a hazard ratio of $\geq$1.7 at an alpha of 0.05 (two sided) over a 20-year follow-up period. It is estimated that the initial recruitment of 600 participants will have a natural dropout rate of approximately 10% every 5 years. This would result in a sample size of approximately 400 at 20 years, and therefore still be sufficient to identify differences in composite CVD endpoints between the groups.

Sample size calculations were also performed for the other primary study outcomes; cardiovascular risk as determined by pulse wave velocity, and osteoarthritis as determined by

radiograph, each of which required smaller sample sizes than the sample size required for the primary composite CVD end-point analysis.

Statistical methods

The characteristics of non-responders – at recruitment and at follow-up - will be examined and compared to those who (continue to) participate. Differences between responders and non-responders will be examined with logistic regression analysis. Response weights will be generated to compensate for unequal probabilities of response based on any significant differences between responders and non-responders on age, rank, service and deployment.

The association between CVD and exposure will be assessed using the chi-squared or Fisher's exact test where appropriate. T-tests and one-way ANOVA will be used to evaluate the association between CVD risk and exposure. Multiple comparisons will be assessed using the Bonferroni correction or similar when appropriate. At baseline, multivariable linear regression will be used to assess the association between primary outcomes and exposure. Generalized Linear Models with a binomial distribution will be used to assess the relative risk of CVD. If the model does not converge then a Modified Poisson Regression approach would be considered. Multicollinearity will be assessed using the Variance Inflation Factor regression diagnostic test.

For repeated measures (baseline, 3, 6 and 10 years), we will use mixed effects models. Cox proportional hazard models will be used to evaluate the association between exposure and disease development over time whilst adjusting for confounders.

Multiple imputation [133] will be considered for missing data. A priori confounders will be adjusted for in the analysis and any other potential confounders will be considered using univariable analyses. A p-value of <0.05 will be considered statistically significant. Data will be analysed using STATA version 16 (Stata Corp, College Station, Texas, USA) with the svy command to take account of the sample and response weights.

Data Storage and Retention

All data will be handled in accordance with current legislation, at present the GDPR 2018 and the Data Protection Act 2018. Physical data will be pseudoanonymised and stored accessible only by the research team. Digital data will be secured using dedicated data management software. After the last participant's final follow-up, all data will be stored for a minimum of 15 years.

Ethics and dissemination

The ADVANCE Study has Ministry of Defence Research Ethics Committee (MODREC) approval (protocol No:357/PPE/12), granted on 15th January 2013. The trial will be performed in accordance with the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. Results will be disseminated through manuscripts in clinical/academic journals, presentations at clinical/academic conferences and communications with participants and other stakeholders and via the ADVANCE study website www.advancestudydmrc.org.uk.

Participant Involvement

Ex-patients of DMRC Headley Court were involved in the development and design of the study from the outset as were a number of experienced clinicians regarding appropriate outcomes, feasibility, tolerability, priorities and recruitment. Ongoing participant consultations continue to influence recruitment, outcome measure priorities and acceptability.

Authors' contributions:

The study concept and design were conceived by ANB, CB, AB, NF and PC.

ANB and DD were the main authors of the paper. SS provided significant portions of the data analysis section and provided critical revisions to the whole paper. NF, CB, AB and PC provided critical revisions to the whole paper.

Final approval of the whole paper was given by all authors. All authors agree to be accountable for all aspects of the accuracy and integrity of this protocol paper.

Funding statement

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Acknowledgements

We wish to thank all the nursing and ancillary staff who have helped with the ongoing ADVANCE Study. We would like to acknowledge in particular our senior research nurses Helen Blackman, Louise Young and Seamus Wilson, and our project managers Maria-Benedicta Edwards, Melanie Chesnokov, Maija Maskuniitty and Emma Coady.

Competing interests' statement

ANB works for the Ministry of Defence

NTF receives funding from the MoD and is a trustee of a veteran charity.

AMJB directs a research centre that receives funding from veteran's charities and is supported by the Ministry of Defence.

Additional complementary methods

ADVANCE cohort:

ADVANCE is an ambidirectional cohort study. The exposure (combat injury) was determined at point of injury, several years prior to the ADVANCE baseline assessment. At baseline assessment, most other variables are cross-sectional in nature, measuring either a retrospective construct (e.g. depression symptoms over the past two weeks) or current measurement at time of assessment (e.g. cholesterol levels). Prospective areas of investigation include for example MACE outcomes. As such, analysis is partially prospective from point of sampling and retrospective from the baseline assessment of the study.

IMPACTS procedure:

Confirmation of ethical approval from the UK Ministry of Defence Research Ethics Committee for the IMPACTS study was received in May 2018. From that time point, all participants completed the IMPACTS questionnaire, which included the DPTGI and other self-report health questionnaires not used in this thesis (Chapter 2 Supplementary Materials 1) as part of their ADVANCE study day. All participants who had already taken part in the study (n=580) were invited to complete the questionnaire via post or online. Participants were invited via a mixture of email, postal and text invitations with either personalised links to the online portal of the questionnaire or physical copies of the questionnaire with postage-paid return envelopes.

Factor structure of measures:

Post-traumatic stress disorder CheckList-Civilian version (PCL-C) factors

The PCL-C was used to assess PTSD symptoms. Symptom clusters were based on the DSM-IV classification of PTSD and included factors of avoidance behaviours, emotional numbing, intrusive thoughts and hyperarousal (141). Details of which items belong to which cluster can be found in Chapter 2 Supplementary Materials 2.

Deployment-related Post-Traumatic Growth Inventory (DPTGI) factors

The DPTGI was used to assess PTG. The five factors of PTG were used and included appreciation of life, personal strength, new possibilities, relating to others and spiritual change (142). Details of which items belong to which factor can be found in Chapter 2 Supplementary Materials 3.

Data analysis

Several data analysis procedures were used to address the aims of this thesis. Chapters three-six explain how the specific data analysis procedures were used to address these aims as applied to the ADVANCE cohort dataset. In this chapter I will briefly introduce these statistical techniques.

Logistic regression

Logistic regression is a modelling technique whereby the conditional probability of an independent variable is measured as a function of a discrete/binary dependent variable. For example, a logistic regression might be used to investigate the probability that socioeconomic status (the independent variable) is associated with depression (the dependent variable). In this example, depression is coded as 0 (no depression) and 1 (depression). Logistic regression computes coefficients of the proposed model in the metric of log odds, which can be exponentiated to create odds ratios. Odds ratios are beneficial as they increase the interpretability of the explored model. In a logistic regression, the odds ratio is informed by the model, so represents the constant effect of the independent variable (socioeconomic status) on the likelihood of the dependent variable (depression).

To conduct a logistic regression, certain assumptions of the model need to be met. These include independence of errors, linearity in the logit, absence of multicollinearity, and no outliers in the residuals (143). Independence of errors indicates that no relationship/correlation between the residuals is present in the model. Linearity in the logit refers to the assumption that there is a linear relationship between the independent and dependent variables (144). Multicollinearity refers to strongly correlated independent variables. The presence of multicollinearity can inflate/deflate the coefficients. Residuals in a model should follow a normal distribution around 0. If there are outliers in the residuals, e.g. residuals far to the left or right of 0, these can have strong effects on the coefficient and ultimately the interpretation of the model (Chapter 2 Figure 4).

The strengths of the logistic regression approach include a relatively straightforward set of underlying assumptions that are easily applicable to many types of datasets and allows for easy interpretation from odds ratios. There are, however, some limitations to the approach. Researchers must be careful when interpreting the results of logistic regression models as odds ratios, as the language is often mis-interpreted due to confusion between risk and odds (145). It is not recommended to control for mediating factors between the independent and

dependent variable in logistic regression modelling, which is best suited to other methodologies (e.g. structural equation modelling) (146). Finally, logistic regression modelling assumes a linear relationship between independent and dependent variable, which may not exist (e.g. non-linear relationships such as a u or inverted-u shaped curve).

Multinomial logistic regression

Multinomial logistic regression is an extension to logistic regression which can be used when there are additional discrete values to the dependent variable. Following our previous example, multinomial logistic regression would be appropriate if we were to investigate the probability that socioeconomic status (the independent variable) is associated with PTG (the dependent variable), where PTG has multiple levels, e.g. 0 (no/a low degree of PTG) 1 (a moderate degree of PTG) 2 (a large degree of PTG). Using multinomial logistic regression, instead of computing odds ratios, we can compute Relative Risk Ratios (RRR). RRR in multinomial logistic regression are calculated on the constant effect of the independent variable (socioeconomic status) on the likelihood of the dependent variable at separate levels. In our example, the RRR of socioeconomic status at the moderate degree of PTG and large degree of PTG levels can be computed relative to the no/a low degree of PTG level.

The strengths of multinomial logistic regression mimic that of logistic regression modelling, with the extension that multinomial logistic regression allows for the calculation of RRR, an intuitive and highly interpretable statistic.

Robust regression: MM-estimator

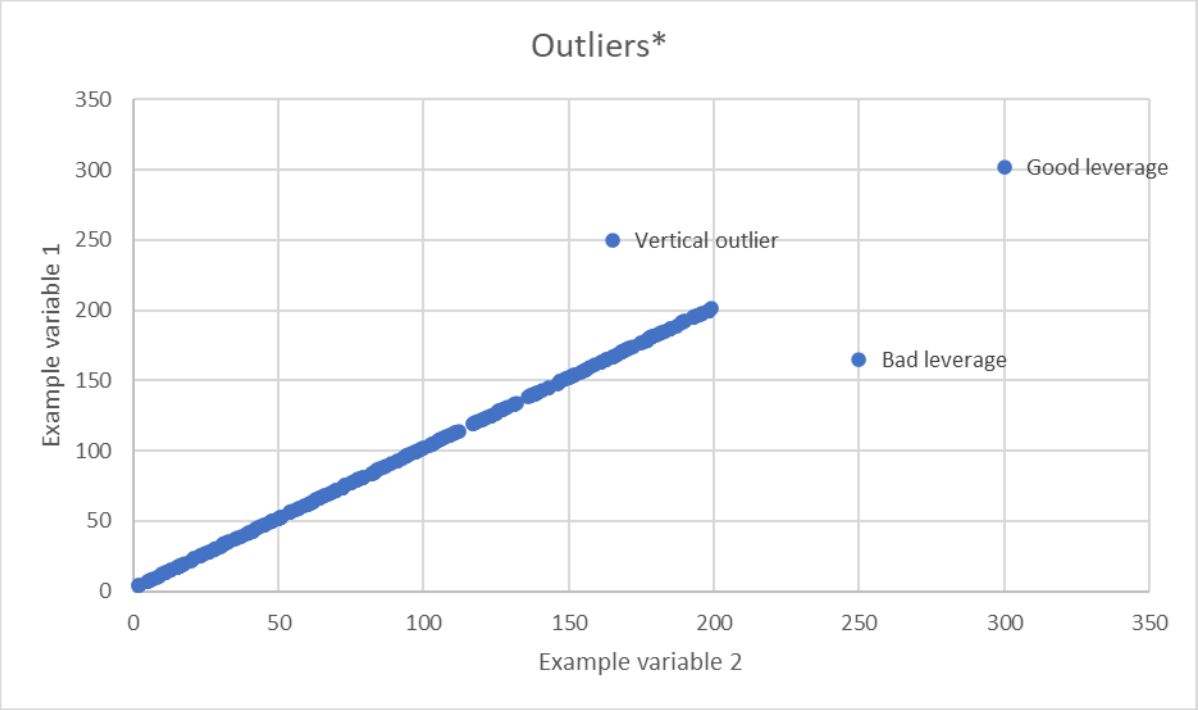
Regression modelling attempts to create models that mimic the true value of the observations through implementation of aggregate prediction error, i.e. by reducing the magnitude of the impact from residuals on the model. In linear, logistic and multinomial regression, this is defined as the sum of the squared residuals. However, this method of addressing residuals puts enormous importance on large residuals (e.g. outliers), meaning outliers have a larger input on the parameters of the model than non-outliers (Chapter 2 Figure 4). This is particularly problematic when these outliers exist and they cannot be controlled for or excluded, e.g. if the outliers were categorically similar based on a trait such as amputation injury, you might decide to exclude them or adjust your model to account for these types of outliers. Robust regression is used to address this issue, by applying weights to the highly influential observations.

Robust regression can be completed using different equations to calculate the weighting of the residual outliers (147). Robust regression with M-estimator is a function of generalised median regression, by which aggregate prediction errors are still calculated by the squared sum of residuals but iteratively re-weighted. This gives protections against vertical outliers, however this methodology does not protect against bad leverage points[8]. Robust regression with S-estimator changes the calculation of the aggregate prediction error from the sum of the squared residuals to a different loss function, one of the most popular being the Tukey biweight function. Whilst this method is better than M-estimators at protecting against all types of outliers, it has low efficiency (e.g. poor relative efficiency of robust estimates compared to a linear regression model with normal residual distribution of no outliers) or poor breakdown values (e.g. the proportion of outliers that can be addressed before they overly influence the model). Robust regression with an MM-estimator is a method of robust regression which attempts to retain a high break-down value and efficiency by combining methodology of the M-estimator and S-estimator.

The strengths of this approach include the ability to include all observations without the need to dismiss those that heavily influence the model and the high breakdown and efficiency of MM-estimator robust regression methodology, which has been shown to be one of the best performing robust regression methodologies currently in use (148). One limitation is that despite these methods being relatively easy to apply in most statistical packages, they are not regularly used in the general literature, and social scientists as a result are hesitant to use these methodologies (149).

[8] *For a review of outlier types, please see chapter 2 figure 4: Example outliers (pg. 135)*

CHAPTER 2 FIGURE 4: EXAMPLE OUTLIERS

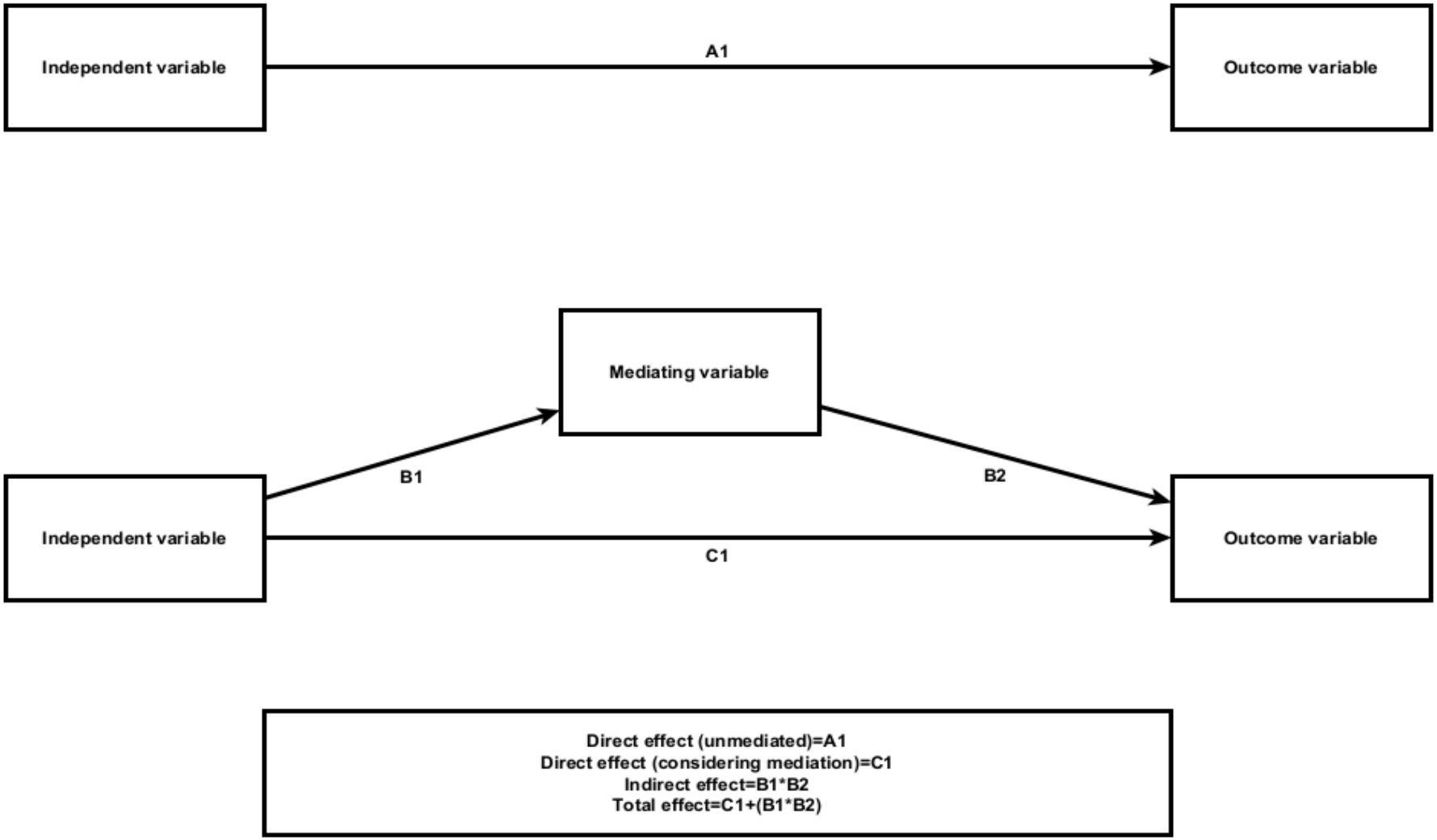


**Vertical outliers refer to outliers on the y axis. Bad leverage refers to outliers on the x axis. Good leverage refers to outliers on/near the predicted coefficient line, but far away from most other observations.*

Generalised Structural Equation Modelling (GSEM): mediation analysis

Structural Equation Modelling (SEM) is a multivariable statistical analysis approach to assess observed and latent variables (150). Causal inferences can be made between variables using SEM which utilise factor analysis, path analysis and regression modelling. Mediation analysis is an investigation into the effects of an independent on a dependent/outcome variable, both directly and indirectly through a third, mediating variable (Chapter 2 Figure 5) that can be utilised through SEM. In mediation analysis we can calculate the direct effect (the effect the independent variable has on the dependent variable alone), the indirect effect (the effect that the independent variable has on the mediating variable * the effect that the mediating variable has on the dependent variable) and the total effect (the direct effect + the indirect effect).

CHAPTER 2 FIGURE 5: MEDIATION



GSEM is utilised in this thesis to address the aims of assessing mediation and to allow for the fitting of ordered logistic and binary measurements (e.g. categorical). GSEM also allows for multilevel analysis through multinomial logistic regression modelling. GSEM is a better technique for mediation analysis compared to other regression based counterparts due to its causal inference properties, by which the indirect and direct effect as well as the dual role of mediator variables as both cause and effect are suitably accounted for in SEM but more difficult to express in standard regression (6). In addition to assumptions of a general linear model, mediating analysis requires; temporal precedence among the variables (e.g. the independent variable occurred before both the mediating and outcome variable), no bidirectional relationships (e.g. the outcome cannot cause the mediator, constructing a feedback loop), measurement error in the mediator, and specification error (e.g. variables are omitted from the model) (150, 151).

Benefits of GSEM include visual aids to interpretation of models, that are easily accessible by readers. GSEM also allows for the assessment of direct, indirect and total effect, making it a strong statistical approach for assessing mediation. Limitations of the approach include an inability to truly assess variables with feedback loops/bidirectional relationships. For example, assessing the effect of depression on heart rate through physical activity levels would be difficult, as depression reduces likelihood of physical exercise and not engaging in physical exercise increases likelihood of depression.

Bootstrapping

Ideally, studies will aim for a large enough sample size so that they can assume the sampling distribution is normally distributed (152). This assumption is necessary to run many parametric statistical approaches, including regression analyses. However sometimes getting a large sample size may be difficult, perhaps due to investigation of relatively rare phenomena. Assuming that the sample drawn from the population is representative of the population under investigation, one may choose to use bootstrapping. Bootstrapping is a re-sampling statistical method by which a dataset is simulated and recreated many times. By doing so, we can estimate a sampling distribution with a more reliable standard error (153). The size of the original dataset is still crucial, as re-sampling using bootstrap does not increase the amount of information in the dataset. Bias-corrected bootstrapping is used in this thesis for all methods of analysis, including logistic regression, robust regression, GSEM and variable selection procedures to derive more precise confidence intervals. Bias corrected

confidence intervals account for any bias in the bootstrap parameter estimates (e.g. any bootstrap estimates less than the original parameter estimate) (154).

Strengths of bootstrapping analyses include a more precise estimation of confidence intervals without introducing model instability (153). Alongside these benefits of bootstrapping, bootstrapping can be applied in a wide variety of data analytical approaches as it does not have any underlying assumptions of the distributions of the data. Limitations of the approach include the necessity for the sample size to be representative of the population, e.g. a large enough sample size still needs to be drawn otherwise accuracy of the bootstrap estimates will be undermined (154).

Variable Selection Procedures: Bootstrap Inclusion Frequencies (BIF)

A part of the process of scientific inquiry using statistical modelling is deciding which variables to include in the model employed to assess your hypothesis. Usually this includes hypothesis generated variables as well as a-priori confounder variables, e.g. those variables which have previously been found to be associated with the independent variable and dependent variable. However, when there are multiple hypothesis generated variables, the researcher must decide which variables should be included in their final model. Stepwise regression is one such process. Stepwise regression can be completed as a forward selection (by which the independent variables of interest are added one at a time to a known model and are retained if certain selection criteria are satisfied, e.g. $p<.05$) or backward selection (by which all independent variables of interest are added at the same time to a known model, and individually removed based on selection criteria). However, this process has been shown to lead to underestimating of the standard errors, which in turn leads to narrower confidence intervals and lower p-values when in truth, these values should be much higher (155-157).

One method to increase model stability in variable selection is by using BIF. Variable selection procedures utilising BIF resample the observed data in a simulated dataset and assess how many times a variable achieves a certain selection criteria (e.g. $p<.05$) in these resamples. The more times the variable is resampled and maintains the selection criteria, the higher its associated BIF, and the more likely the independent variable is associated with the dependent variable.

As part of variable selection procedures, it is recommended that assessment of whether variables are competing for inclusion (also known as co-dependence), i.e. assessing which of multiple correlated variables should be included in a model (18). For multiple correlated

variables with weak/moderate associations with the dependent variable (e.g. BIF >0.30), it is suggested to assess whether the two variables are competing for inclusion by investigating the 2x2 frequency table of associated BIF for the two variables and computing a chi^2 analysis. Variables which do not reject the independence hypothesis remain in the model. For variables that are assessed as co-dependent, further scrutiny of the times that each variable is included in the model is warranted. First, variable one (x_a) is assessed and removed if either condition from *Equation 1* or *Equation 2* holds true based on tuning parameters for weak associations. The steps are then repeated for variable two (x_b). If both variable one and two satisfy one of the two conditions, the variable with the smaller BIF value is removed.

EQUATION 1: ASSESSMENT OF CO-DEPENDENCE, CONDITION 1

$$BIF(x_a) > 1.4 * BIF(x_a|x_b)$$

EQUATION 2: ASSESSMENT OF CO-DEPENDENCE, CONDITION 2

$$BIF(x_a|x_b) > 1.4 * BIF(x_a)\ \&\ BIF(x_a) < 1.4 * 0.3)$$

Strengths of using BIF as well as assessment of co-dependence has the beneficial property of maintaining the highest explanatory ability of the end result model without increasing model instability and ensuring parsimony (158). Limitations of BIF include that it is a data dependent model building exercise which may exclude pertinent variables if other co-variates are not included in the model e.g. assessment of multiple co-dependent variables or non-inclusion of pertinent confounders. Also, whilst incorporation of non-linear relationships is possible in BIF, greater research is required on their effects on variable selection procedures (156, 157).

Variable Selection Procedures: Weighted Average Least Squares (WALS) model averaging

Model averaging is a process of estimating a model, followed by averaging (e.g. median) the model estimate based on the likelihood that the model is true. By doing so, one can compare several models and assess the likelihood that each model truly fits the data. Bayesian model averaging computes the weighted average posterior probability of each model and chooses the model with the highest average. Frequentist model averaging may use different estimators based on the data dependent diagnostic criterion rather than the posterior probability of each model, e.g. exponentiated Akaike information criteria or minimisation of a Mallows criterion (159). WALS model averaging uses a combination of both Bayesian and frequentist model averaging (160) utilising constrained least squares to estimate the parameters of the model (frequentist approach) and subsequent weighting based on a Bayesian approach. This allows

for a computationally less burdensome and strong theoretically grounded approach to model averaging (161).

Model averaging is a second step recommended for variable selection procedures following assessment of BIF to address model uncertainty (156). Using a two-step variable selection procedure, first using BIF to select independent variables with high likelihood of being related to the dependent variable, then model averaging, incorporates model uncertainty into the selection process and adds additional control parameters (e.g. BIF>0.30 in step one and t score <-1|>1 with standard error bands that do not cross zero in step two), ensuring sufficient likelihood that the independent variables are associated with the dependent variable and are not spurious relationships (156, 160).

Strengths of WALS model averaging include addressing uncertainty in selected models, a reduction in potential estimate error and the fact that WALS has been found to perform well in simulation studies (160, 161). Limitations mimic those of BIFs, including that the methodology is data dependent and rely heavily on the other variables included in the model.

ADVANCE baseline recruitment:

Data collection for baseline assessment started in August 2015 and ended in August 2020. Data collection was put on hold between February 2020 and August 2020 due to the COVID-19 pandemic. Chapter 2 Figure 6 describes the recruitment procedure and participants who did/did not take part in the ADVANCE baseline study. The initial aim of the sample size was 1200 participants (600 injured and 600 uninjured personnel). Due to the external circumstances of the COVID-19 pandemic, it was decided that a small deviation in the aimed sample size was necessary to reduce complications from an elongated recruitment period for baseline, without jeopardising the original power calculations. 579 injured personnel and 566 of the uninjured comparison group were recruited, resulting in a total of 1145. One participant sustained injury un-related to military deployment; this participant is excluded from the analyses in this thesis.

ADVANCE baseline demographics:

The uninjured group were frequency matched to the injured group at point of sampling based on age, service, rank, role, regiment and deployment; however, in those recruited for the ADVANCE cohort study some statistically significant differences were noted based on age, rank, combat role and deployment era (Chapter 2 Table 3). The median age of the injured and uninjured groups differed by one year, which is unlikely to be clinically meaningful. A

greater percentage of higher-ranking individuals were in the uninjured group (SNCO 26.0%; Officer rank 13.9%) compared to the injured group (SNCO 18.3%; Officer rank 10.2%). A greater percentage of participants held combat roles in the injured group (84.5%) compared to the uninjured group (79.7%), and a greater percentage of combat service/-support roles were observed in the uninjured group (20.1%) compared to the injured group (14.7%). The uninjured group reported more deployments in the later deployment eras (HERRICK 11-15 and HERRICK 16-20) compared to the injured group. Uninjured personnel had a higher rate of deployment to HERRICK (median deployments to Afghanistan 2 (IQR 1,2)) compared to the injured group (median deployments to Afghanistan 1 (IQR 1, 2)) which is likely due to the fact that many of the injured group were medically discharged and unable to re-deploy.

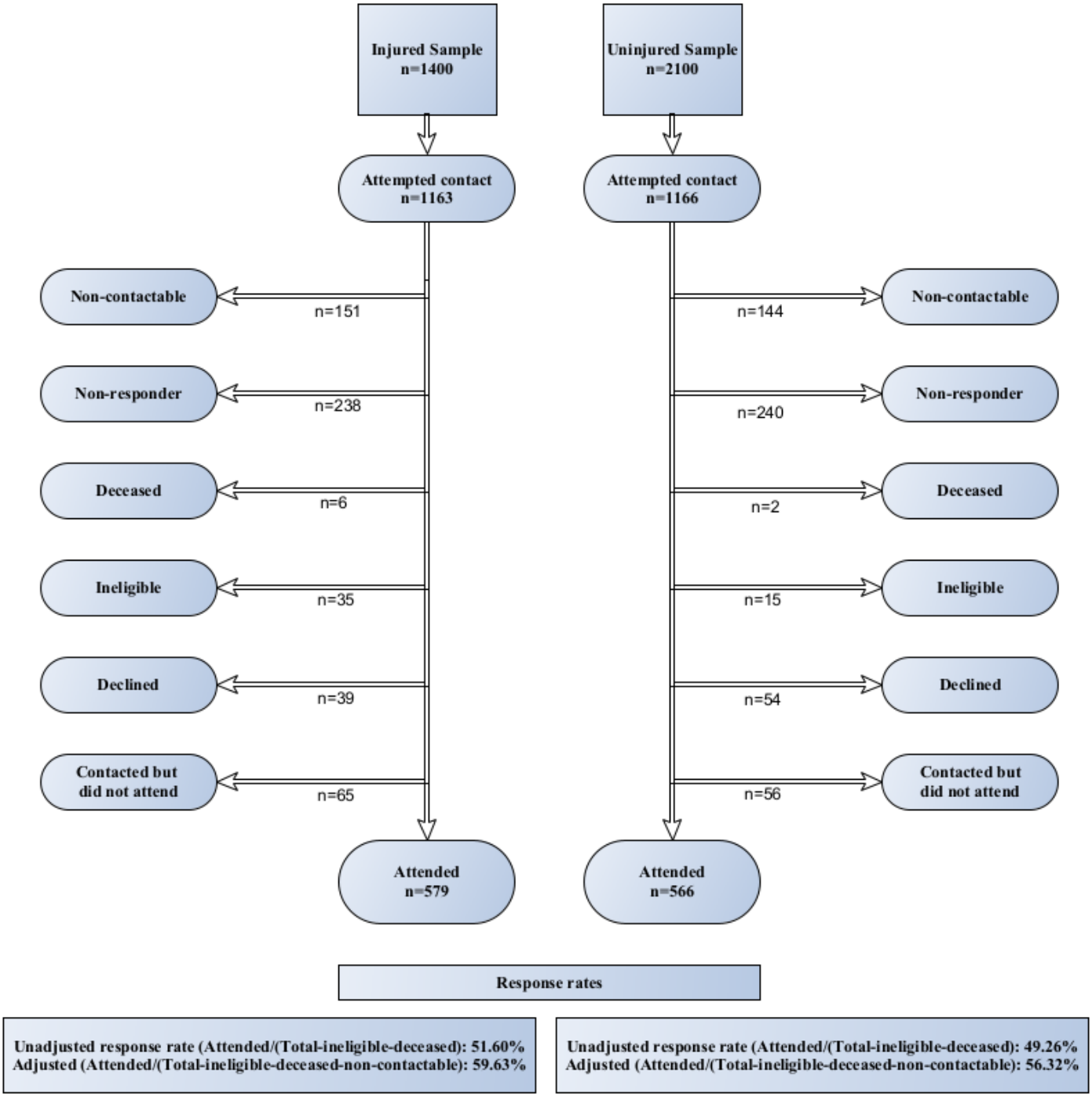
161 of the injured group sustained an amputation injury and 418 sustained a non-amputation injury. Medical conditions reported during the injury period (0-6 months post injury) were categorised by area of the body affected and mechanism of injury (Chapter 2 Figure 7). Greater rates of blast injury were present in participants who sustained an amputation injury (95.0%) compared to those who sustained a non-amputation injury (69.2%). Greater rates of gunshot injuries and other injuries were present in participants who sustained a non-amputation injury (30.1% and 1.4%) compared to those who sustained an amputation injury (5.3% and 0.6%). Participants with amputation injuries reported greater rates of upper limb injuries, torso, genitourinary, and lower limb injuries compared to those who sustained non-amputation injuries. The median NISS[9] between amputation injured and non-amputation injured sub-groups is reported in Chapter **2 TABLE 3** and histograms of the distribution of NISS scores between the amputation injury subgroup and non-amputation injury subgroup can be found in Chapter 2 Figure 8 and Chapter 2 Figure 9.

Details of participants who completed the IMPACTS questionnaire, including demographic differences between those who completed on the day, completed after their ADVANCE study day, or did not complete, can be found in Chapter 2 Figure 10. 1037 participants (90.1% of the overall ADVANCE cohort) completed the questionnaire. Two participants had >3 items missing on the DPTGI. 90.0% (*n*=521/579) of the overall injured group, 85.0% (*n*=138/162) of the amputation subgroup and 91.6% (*n*=383/418) of the non-amputation injury subgroup completed the DPTGI. No statistically significant differences were noted between the groups with regards to completion rates of the DPTGI (for more details, please see chapter four pg.

[9] *New Injury Severity Score (NISS), a measurement of anatomical injury using the three most severely injured body regions.*

200-203). 90.8% (*n*=514/566) of the uninjured group completed the DPTGI. 27.0% of the sample completed the DPTGI ≥12 months after their ADVANCE study appointment.

CHAPTER 2 FIGURE 6: RECRUITMENT PROCEDURE FOR ADVANCE COHORT STUDY



Terms: N**ON-CONTACTABLE** Address/contact details were incorrect/out of date and no new contact details could be found. **NON-RESPONDER** Four invitations were sent to address without response. **INELIGIBLE** Participant was excluded from the study due to not meeting eligibility criteria. **CONTACTED BUT DID NOT ATTEND** Did not attend appointment (includes both participants who arranged appointments and did not attend

and participants who contacted/were successfully contacted by the study team, did not decline but also did not complete booking). **DECLINED** Participant declined to take part in the study.

CHAPTER 2 TABLE 3: SAMPLING DEMOGRAPHICS OF INJURED/UNINJURED GROUPS RECRUITED TO THE ADVANCE COHORT STUDY INCLUDING CHI^2 ANALYSIS FOR CATEGORICAL DATA AND T-TESTS FOR CONTINUOUS DATA

Demographic	**Overall cohort**	**Uninjured group**	**Injured group (Overall)**	**Injured group (Amputation injury)**	**Injured group (Non-amputation injury)**
Age at sampling (years) median IQR	25.0 (22.0, 29.0)	26.0 (23.0, 29.0) *	25.0 (22.0, 29.0) *	25.0 (22.0, 28.0) *	25.0 (22.0, 29.0) *
Age at assessment (years) median IQR	33.0 (30.0, 37.0)	34.0 (30.0, 37.0)	33.0 (30.0,37.0)	32.5 (30.0, 36.0) *	33.0 (30.0, 38.0)
Rank n (%)					
Junior Non-Commissioned Officer	754 (65.9)	340 (60.1)	414 (71.5) *	127 (79.4) *	287 (68.5) *
Senior Non-Commissioned Officer	253 (22.1)	147(26.0)	106 (18.3) *	20 (12.5) *	86 (20.5) *
Officer	138 12.0)	79 (13.9)	59 (10.2) *	13 (8.1) *	46 (11.0) *
Service branch n (%)					
Naval services/Royal Marines	53 (14.1)	84 (14.8)	77 (13.3)	~	~
Army	947 (82.7)	463 (81.8)	484 (83.6)	~	~
Royal Air Force	37 (3.2)	19 (3.4)	18 (3.1)	~	~
Serving status n (%)					

Demographic	**Overall cohort**	**Uninjured group**	**Injured group (Overall)**	**Injured group (Amputation injury)**	**Injured group (Non-amputation injury)**
Serving	624 (52.4)	466 (82.2)	421 (73.0)*	17 (10.4)*	141 (32.7)*
Veteran	520 (47.7)	99 (17.8)	158 (27.0)*	144 (89.6)*	277 (67.3)*
Role on deployment n (%)					
Combat role	940 (82.1)	451 (79.7)	489 (84.5) *	134 (83.8) *	355 (84.7)
Combat support/Service role	199 (17.4)	114 (20.1)	85 (14.7) *	25 (15.6) *	60 (14.3)
Other/Missing	6 (0.5)	1 (0.2)	5 (0.8)	1 (0.6)	4 (1.0)
Deployment era* n (%)					
HERRICK 0 (2002-2004)	NR	NR	NR	NR	NR
HERRICK 1-5 (2004-2007)	149 (13.0)	70 (12.4)	79 (13.6)	18 (11.3)	61 (14.6)
HERRICK 6-10 (2007-2009)	579 (50.6)	296 (52.3)	283 (48.9)	69 (43.1) *	214 (51.1)
HERRICK 11-15 (2009-2012)	751 (65.6)	406 (71.7)	345 (59.6) *	97 (60.6) *	248 (59.2) *
HERRICK 16-20 (2012-2014)	334 (29.2)	216 (38.2)	118 (20.4) *	21 (13.1) *	97 (23.2) *
Number of deployments to HERRICK median (IQR)	2 (1, 2)	2 (1, 2)	1 (1, 2) *	1 (1, 2) *	1 (1, 2) *
New Injury Severity Score (NISS)	NA	NA	13 (5, 30)	34 (21, 48)	9 (4, 18)

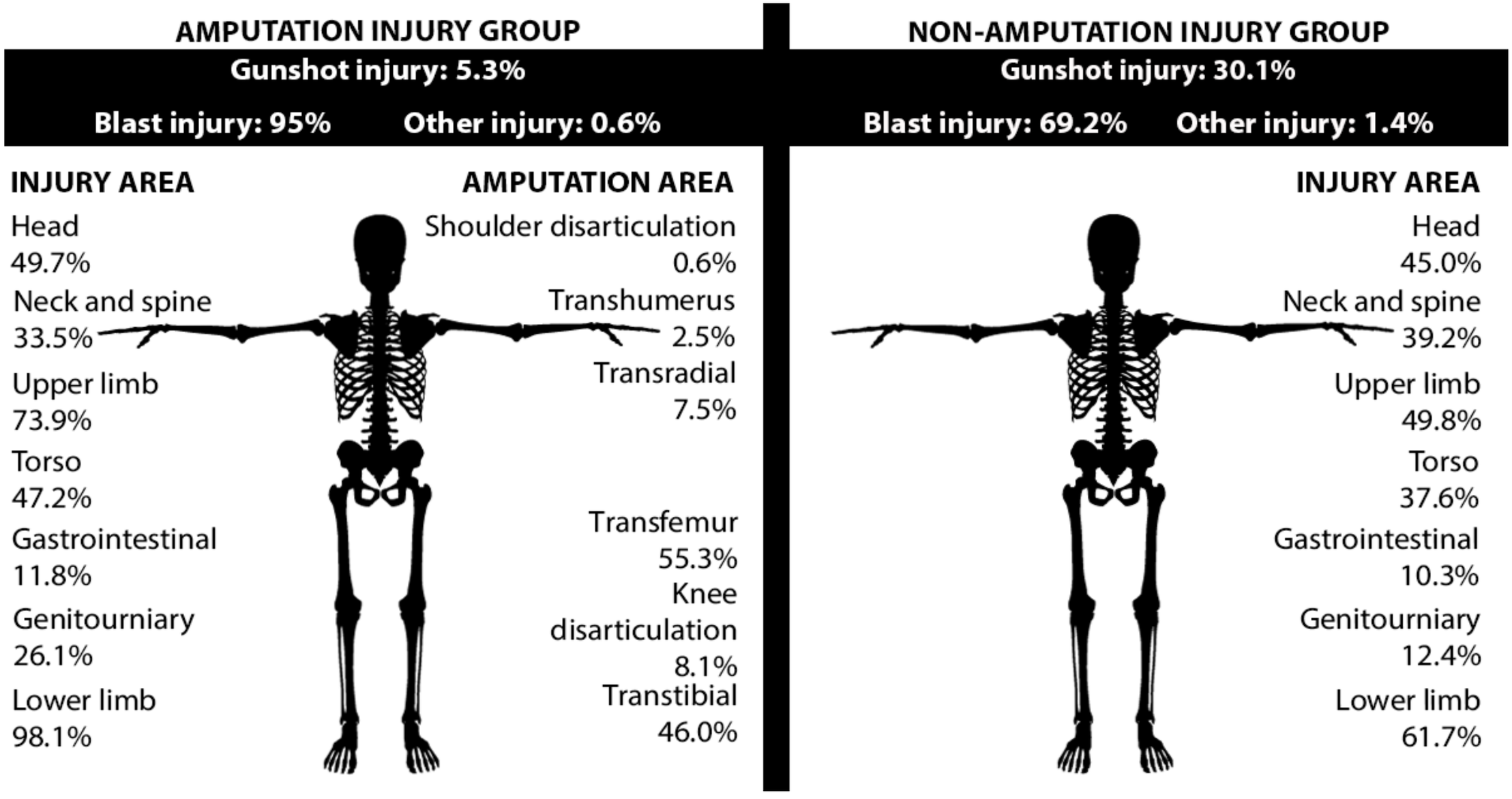
Demographic	**Overall cohort**	**Uninjured group**	**Injured group (Overall)**	**Injured group (Amputation injury)**	**Injured group (Non-amputation injury)**

***** indicates significant difference at $p<.05$. Analysis was completed comparing rates of each injured group compared to the uninjured group.

Percentages will not add up to 100% as participants may have deployed to multiple eras.

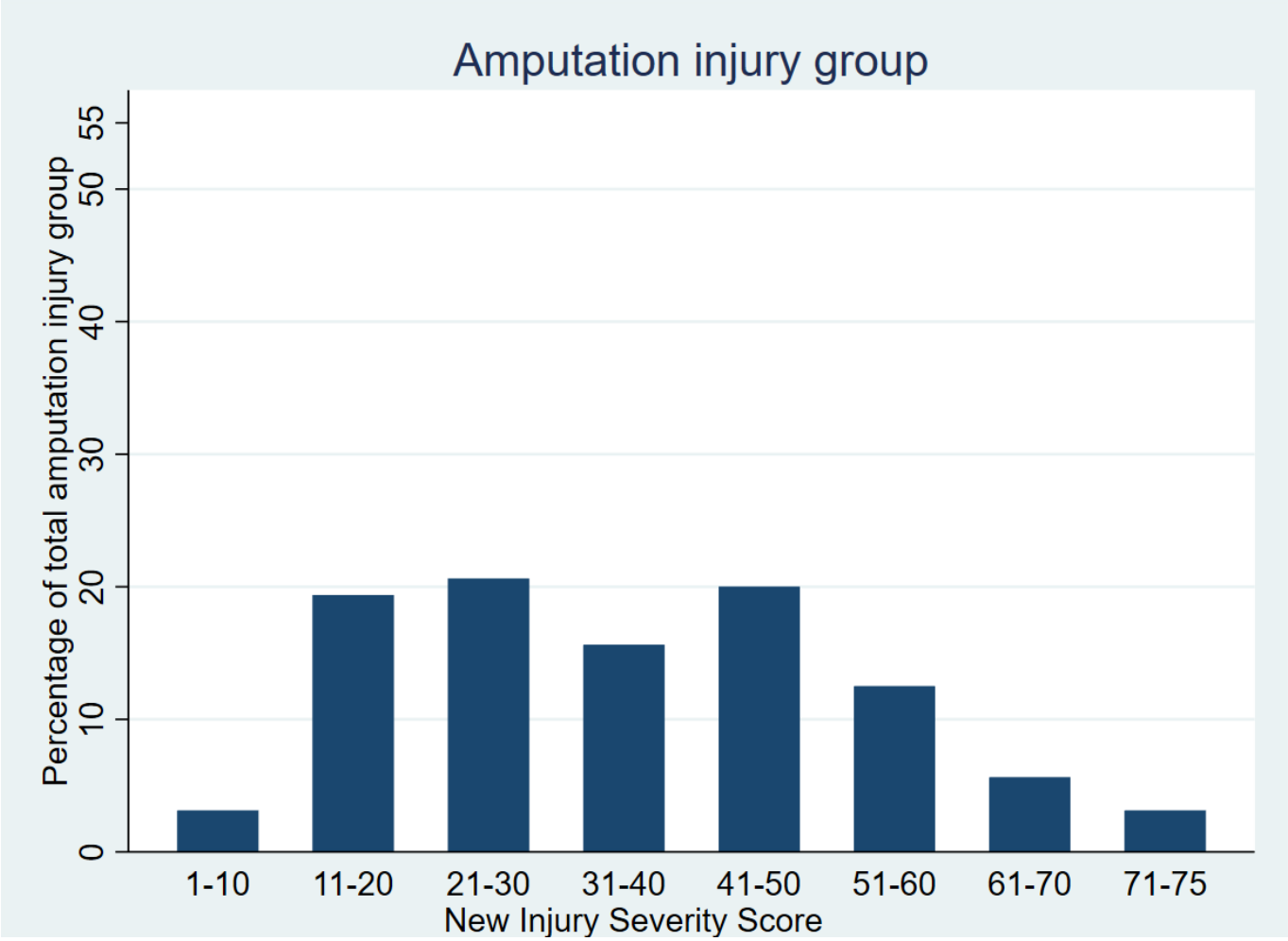
~ Some data on injuries sustained whilst on deployment are suppressed to allow for medical confidentiality of the survivor in line with Defence Statistics rounding policy (https://www.gov.uk/government/publications/defence-statistics-policies/ministry-of-defence-disclosure-control-and-rounding-policy).

CHAPTER 2 FIGURE 7: MECHANISM AND BODILY REGION OF INJURY STRATIFIED BY AMPUTATION INJURY (*N*=161) AND NON-AMPUTATION INJURY (*N*=418) GROUPS

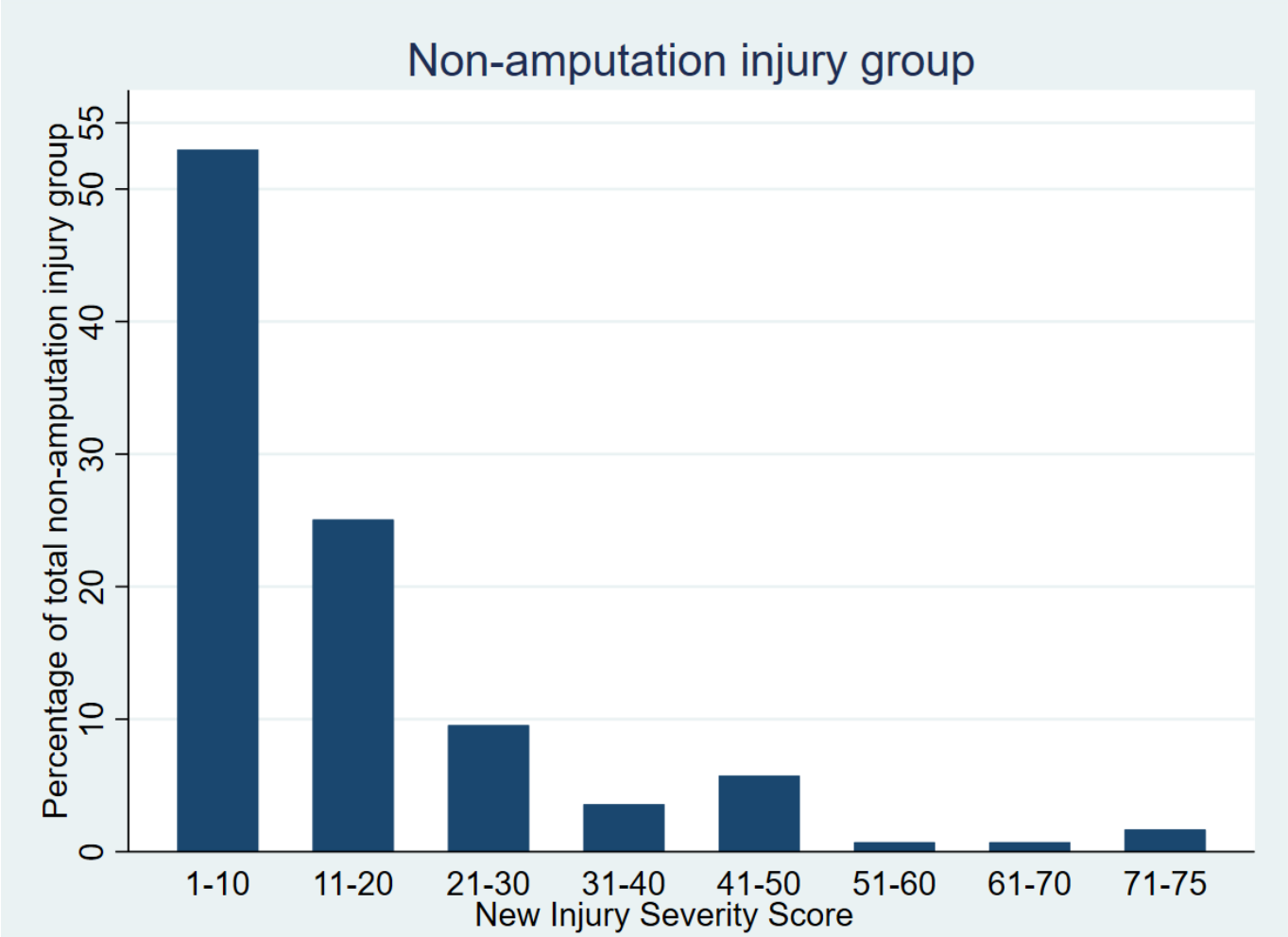


**Participants may have injuries on multiple areas of the body or multiple limbs amputated. Participants may experience a mixture of blast, gunshot and/or other mechanisms of injury.*

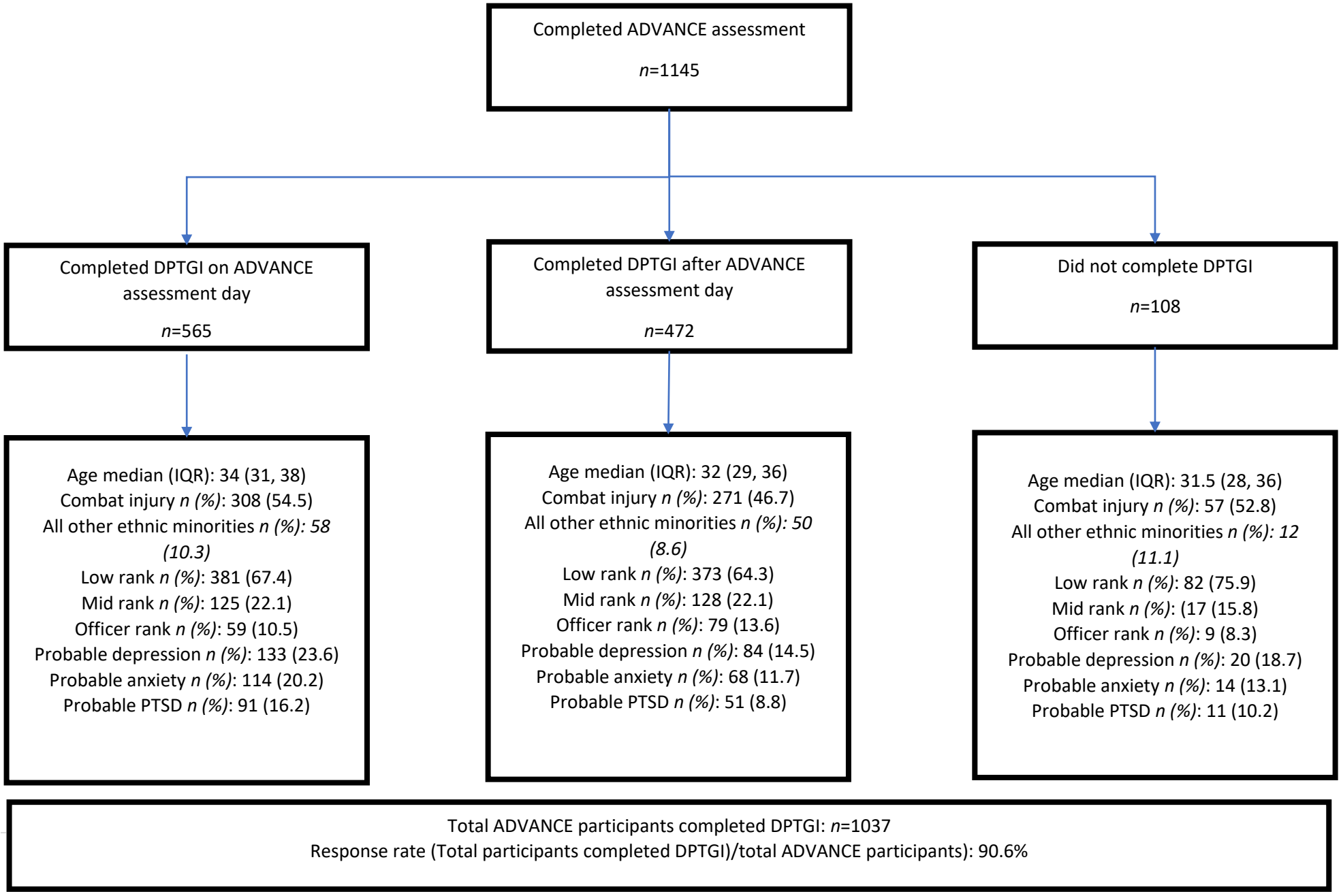
CHAPTER 2 FIGURE 8: DISTRIBUTION OF AMPUTATION INJURY SUBGROUP NEW INJURY SEVERITY SCORES (N=161)



CHAPTER 2 FIGURE 9: DISTRIBUTION OF NON-AMPUTATION INJURY SUBGROUP NEW INJURY SEVERITY SCORES (N=418)



CHAPTER 2 FIGURE 10: NUMBER AND DEMOGRAPHICS OF PARTICIPANTS WHO DID/DID NOT COMPLETE THE DEPLOYMENT-RELATED POST-TRAUMATIC GROWTH INVENTORY



Key messages

Who is the group that the study will gather data from?

- Injured personnel were selected for the study based on details from several military systems, including the Joint Theatre Trauma Registry, Headley Court prosthetics database and Defence Statistics medical records. Those who sustained an amputation injury were selected first, then those who sustained very serious/serious non-amputation injuries, and finally a random sample of non-very serious/serious or unclassified injuries.
- Uninjured personnel were frequency matched to the injured group based on age, service, rank, regiment and role on deployment.

What data will be gathered and how will it be analysed?

- Venous blood sampling, Vicorder, DEXA, X-ray, audiometry, spirometry, six-minute walk and self-report questionnaires (investigating demographic, health-related behaviours, mental health and occupational outcomes) were employed to assess the health and well-being outcomes of the participants. Those who sustained an amputation injury had additional questionnaires (e.g. phantom pain) and an amputation mobility assessment to assess amputation specific aspects of health.
- Statistical procedures including logistic regression, multinomial logistic regression, robust regression, generalised structural equation modelling and variable selection procedures including bootstrap inclusion frequencies and model averaging are used as part of this thesis.

Demographics of the study group:

- 1145 participants took part in the ADVANCE cohort, including 579 injured personnel (161 who sustained an amputation injury and 418 who sustained a non-amputation injury) and 566 uninjured personnel. One participant is excluded from analysis in this paper due to experiencing serious injury not related to military duties.
- 1037 participants completed the IMPACTS questionnaire, though two were excluded due to >3 items missing on the DPTGI. Of the subsequent 1035, 138 sustained an amputation injury (85.0% of the ADVANCE sample), 383 sustained a non-amputation injury (91.6% of the ADVANCE sample) and 514 were part of the uninjured comparison group (90.8% of the ADVANCE sample).

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3
Mental health outcomes of male UK military personnel deployed to Afghanistan and the role of combat injury
"A matter of comparison: whilst our injured group had greater rates of mental illness compared to the uninjured group, both groups reported greater rates of PTSD compared to the UK general population."

Overview

In this chapter, I will attempt to answer aim 1.1 and 1.2 of this thesis by explaining the observed associations between combat injury and probable mental illness, specifically anxiety, depression, PTSD and mental health multimorbidity, using the baseline assessment of the ADVANCE study cohort. The chapter synthesises the existing literature on the topic of combat injury and mental health from deployments to Iraq/Afghanistan, describes the demographics of the ADVANCE cohort as well as the rates of mental illness amongst the overall uninjured group, overall injured group, amputation injury subgroup and non-amputation injury subgroup. This chapter will also discuss some of the findings of this study in context and reasons why differences in rates of probable mental illness exist between those with amputation and non-amputation injuries.

Aim 1.1 Compare the rates of PTSD, depression, anxiety and mental health multimorbidity between injured and uninjured groups of Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).

Aim 1.2 Investigate whether subgroups of the injured group, specifically those who sustained an amputation injury and non-amputation injury, exhibit differences in rates of these outcomes.

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Mental health outcomes of male UK military personnel deployed to Afghanistan and the role of combat-injury: The ADVANCE cohort study

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Conflict of interest

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Abstract

Background: The long-term psychosocial outcomes of UK Armed Forces personnel who sustained serious combat-injuries during deployment to Afghanistan are largely unknown. This study hypothesised that the rates of probable Post Traumatic Stress Disorder (PTSD), depression, anxiety and mental health multimorbidity will be greater among a representative sample of ex-/serving military personnel with combat injuries compared to a matched sample of uninjured ex-/serving military personnel.

Methods: 579 combat-injured and a comparison group of 565 uninjured male UK Armed Forces ex-/serving personnel, frequency-matched by age, rank, regiment, deployment, and role on deployment were included in this analysis. Participants had a median age of 33 (IQR 30, 37) at time of assessment. 90·3% identified as white and 9·7% were from all other ethnic groups. Participants completed a comprehensive health assessment including both physical health assessment and self-reported mental health measures.

Results: The rates of PTSD (16·9% vs 10·5%; Adjusted Odds Ratio (AOR) 1·67 (95% Confidence Interval (CI) 1·16, 2·41), depression (23·6% vs 16·8%; AOR 1·46 (95%CI 1·08, 2·03), anxiety (20·8% vs 13·5%; AOR 1·56 (95%CI 1·13, 2·24) and mental health multimorbidity (15·3% vs 9·8%; AOR 1·62 (95%CI 1·12, 2·49) were greater in the injured versus uninjured group respectively. Minimal differences in odds of reporting any poor mental health outcome were noted between the amputation injury subgroup and the uninjured group, whereas up to double the odds were noted for the non-amputation injury subgroup.

Interpretation: Serious physical combat-injuries are associated with poor mental health outcomes. However, type of injury influences this relationship. Regardless of injury, this cohort represents a group who present with greater rates of PTSD compared to the general population and increased psychological burden from multimorbidity.

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Research in context

Evidence before this study

To investigate the mental health outcomes of physically injured military personnel who deployed to Afghanistan, we searched EMBASE, Global Health, PsycINFO and OVID MEDLINE. Search terms included: ((ex-serving OR armed forces OR military OR soldier OR officer OR combat OR ex-military) AND (Afghanistan OR Herrick OR operation enduring freedom OR Iraq OR Telic OR operation Iraqi freedom OR operation new dawn) AND (PTSD OR PTSS OR mental illness* OR mental health OR mood disord*) AND (injur* OR disab* OR amputat*)). Inclusion criteria were: published between 2001-current (29/08/2021), original research articles, human studies only, must report on samples who deployed to Afghanistan. Exclusion criteria were: primary sample population of severe traumatic brain injuries and female-only samples. No language restrictions were used.

Thirty-four papers were included in this review. Almost all studies were from US military samples (*n*=31), with one study on UK, one study on French and one study on Danish military samples. Rates of probable PTSD in physically injured personnel ranged from 4% to 58% and rates of depression ranged from 3% to 38%. A third of papers focussed on any combat-injuries and the rest focussed on specific injuries (e.g. thermal injuries, amputations) or mechanism of injury (e.g. explosive, gunshot wound). The majority of studies compared against a reference group of other injured personnel (e.g. amputation injuries compared to non-amputation injured). Of those that compared to an uninjured reference group, combat-injury was associated with poorer mental health outcomes. Several studies investigated pain and suggested that it was a mediating factor between injury status and mental health outcomes. Quality of evidence, as assessed by the National Heart, Lung and Blood Institutes quality assessment tools, was adequate.

Added value of this study

This study has a large sample size that is representative of UK military personnel who sustained seriously physical injuries from the Afghanistan deployments, with a frequency matched uninjured group from which to derive a suitable comparison group. The design allows for a more reliable attribution of odds of reporting poor mental health outcomes associated with combat injury due to the study design, which previous studies have lacked.

Implications of all the available evidence

It has been almost 20 years since the UK started Operation HERRICK (the military operations in Afghanistan between 2002 and 2014). Whilst combat injuries sustained during these operations are related to an increased reporting of poor mental health outcomes, the present findings suggest that the long-term mental health outcomes of combat casualties vary depending on the type of injury sustained during deployment. This study also directs attention to the potential psychological burden of those with mental health multimorbidity. These findings suggest that long term follow-up of those deployed to a combat zone are essential and more attention to the mental health of those with less visible injuries, including pain, is warranted.

Introduction

Military personnel who sustain a combat-injury are at increased risk of poor mental health outcomes, however evidence for the UK military is limited (1-4). The recent conflict in Afghanistan represented a unique period whereby the trauma management was advanced to the point that severely injured personnel were more likely to survive than at any other point in history (5).

The mechanisms by which the UK military personnel sustained injuries in Afghanistan were primarily from Improvised Explosive Devices (IED), rocket propelled grenades and gunshots, which together accounted for over 90% of all UK injuries (6). Lower limb injuries were the most prevalent, followed by upper limb injuries and head injuries. 265 UK military personnel sustained a major limb amputation as a result of their deployment to Afghanistan between 2003 and 2014 (7).

The mental health of military personnel who sustained a physical combat-injury has been researched in the short-medium term. Much of this research is on US samples and suggests that sustaining a physical combat-injury increases the risk of subsequent mental ill health (1, 3, 4, 8). To the authors' best knowledge, the only study in the UK military suggests that, compared to those who deployed and were not medically evacuated during deployment to Iraq/Afghanistan, those who were medically evacuated were at increased risk of post-deployment probable Post-Traumatic Stress Disorder (PTSD) (9). Outcomes vary depending on the type and mechanism of the injury as well as the mental health outcome investigated (1, 3, 10), though many studies do not have data on an uninjured comparison group.

The Armed Services Trauma Rehabilitation Outcome (ADVANCE) cohort study is investigating the long-term impact of sustaining a physical combat-injury during deployment to Afghanistan (2002-2014) on physical and psychosocial outcomes in UK ex-/serving Armed Forces personnel (11). The ADVANCE study hypothesises that combat casualties will have an increased rates of adverse physical and psychosocial outcomes compared to a comparison group of uninjured Afghanistan-deployed Armed Forces personnel.

The primary aim of this study is to compare the rates of PTSD, depression, anxiety and mental health multimorbidity between the injured and uninjured groups of Afghanistan-deployed Armed Forces personnel. A second, additional aim is to examine whether subgroups of the injured group, namely those with amputation and non-amputation related injuries, exhibit differences in the rates of these outcomes. The primary hypothesis of this study is that there

will be increased rates of poor mental health outcomes in the ADVANCE study injured group compared to the uninjured comparison group.

Methods

Study design and participants

This analysis reports on the baseline data from the ADVANCE cohort (11). Injured personnel were recruited from a sample of physically combat-injured personnel from Afghanistan based on records provided from the Ministry of Defence (MoD) Defence Statistics (Health). Eligibility criteria for the injured group were: sustaining a physical combat-injury whilst on deployment to Afghanistan; aero-medical evacuation as a result of the injury resulting in admission to a UK hospital; and no history of cardiovascular, liver or renal disease prior to injury. Uninjured personnel were recruited as a comparison group, comprised of individuals who were frequency-matched to the injured cohort on their age, rank, regiment, deployment during specific deployment periods (based on frequency of deployment periods from which the injured group sustained their injuries), and role on deployment. Eligibility criteria for the uninjured group were: deployment to Afghanistan and sustaining no physical combat-injuries whilst on deployment; no history of cardiovascular, liver or renal disease prior to deployment. Potential participants from both groups and sampling characteristics were extracted from a combination of data sources including the initial Notification of Casualty System (NOTICAS); the Defence Patient Tracking System; the Defence Medical Information Capability Programme (DMICP); the Defence Medical Rehabilitation Centre (DMRC) Complex Trauma Database; the DRMC Prosthetic database; the Joint Theatre Trauma Registry (JTTR); and the Joint Personnel Administration (JPA) database. The ADVANCE study started data collection on 5th August 2015 and completed baseline data collection on 28th August 2020. The sample size was based on a sample size calculation for the primary hypothesis of the ADVANCE study using a primary composite cardiovascular disease endpoint (11).

Procedure

Participants were recruited through postal, email and telephone invitations. For those who had left the military, efforts to trace them were made through electoral roll data, social media, and advertising through military charities. 2329 participants (1163 injured and 1166 uninjured) were invited to a study day at the Defence Medical Rehabilitation Centre (DMRC): Headley Court (August 2015-August 2018) or Stanford Hall (August 2018 onwards). The study comprised of a comprehensive health investigation, including objective health measures (cardiovascular, respiratory, audiological, and musculoskeletal tests), a clinical interview with

a research nurse (sociodemographic information and personal/family medical histories), and self-completed participant questionnaires (musculoskeletal functioning, mental health, occupational history and drug use).

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.

Measures

SOCIODEMOGRAPHIC AND MILITARY FACTORS

Military and sociodemographic information was collected via self-report questionnaire and clinical interview, supplemented by information provided by Defence Statistics. This included data on serving status, length of service, service branch, rank, number of deployments to Iraq/Afghanistan, regular/reservist status and combat role.

COMBAT-INJURY

Information on combat-injury was collected from electronic medical records and supplemented by self-report in the clinical interview. This included type of injury (e.g. amputation) and mechanism of injury (blast, gunshot wound, or other). New Injury Severity Scores (NISS) (12) (scores range 1-75) were extracted from the JTTR. NISS were treated as a continuous variable and also categorised according to likely mortality from major trauma (NISS>=13) (13).

SEQUALAE OF INJURY

AMPUTATION

Amputations were recorded as above/below/through knee for the lower limb and above/below elbow for the upper limb. Isolated partial amputations (e.g. partial foot, partial hand, finger, toe) were not included in the amputee group.

MENTAL HEALTH

COMMON MENTAL DISORDERS

Depression was measured using the Patient Health Questionnaire 9 item (PHQ9), a nine-item self-report questionnaire that records depressive symptoms over the previous two weeks (14). Depression was defined as a score of ≥10 (scores range from 0-27). Anxiety was measured using the Generalised Anxiety Disorder 7 (GAD7), a seven-item self-report questionnaire that records anxiety symptoms over the previous two weeks (15). Anxiety was defined as a score of ≥10 (scores range from 0-21).

PTSD

PTSD was measured using the PTSD Check List (PCL-C) (16), a 17-item self-report questionnaire examining the symptoms of PTSD according to the DSM-IV over the past month. Probable PTSD was defined as a score of ≥50 (scores range from 17-85).

MENTAL HEALTH MULTIMORBIDITY

Mental health multimorbidity was defined as caseness on the PCL-C (score ≥50) in combination with caseness on either the PHQ9 (score ≥10) or GAD7 (score ≥10).

Choice of primary measure

All outcome measures used in this study are brief, easily accessible and psychometrically validated measures regularly used in UK military epidemiological research. Depression and anxiety are common mental health disorders across both the UK general population (17) and Armed Forces (18). PTSD, whilst not common, is seen more often within certain roles in the UK Armed forces including those who deploy in a combat role (18). Multimorbidity represents an outcome with increased psychological burden beyond that of PTSD alone or depression alone (19). See Chapter 3 Supplementary Materials 1 for full details regarding the choice of primary measures.

Data Analysis

Data analysis was undertaken using STATA MP 16.1 (StataCorp LLC, College Station, TX). Ethnicity was recoded into two groups; White and all other ethnic groups combined. Rank at sampling was coded as a proxy for socioeconomic status; lower rank (NATO OR2-OR4), mid rank (NATO OR5-OR9) and officer rank (NATO OF1-OF6) (20).

Sampling weights were applied to the injured group to take into account the under sampling of the less-seriously injured group (NOTICAS system). Response weights were applied based on age, rank, and service at time of injury/deployment of interest to take into account that officers, royal marines and slightly older participants were more represented in those who responded. Response weights were multiplied by sampling weights and applied using the 'svy' command to all frequency tables. Weighted percentages are presented along with unweighted cell counts. Due to only a small number of missing data (range n=2 to n=8), these were handled using casewise deletion.

Sociodemographic and deployment characteristics were examined in the uninjured and injured groups as well as between amputation injury and non-amputation injury subgroups. Logistic regression was used to assess the relationship between injury status and each mental health

outcome. The unadjusted odds ratio (OR) is presented alongside an adjusted odds ratio (AOR) to show the effect of including confounders on the relationship between combat injury and the mental health dependent variables. Conclusions on the aims/hypothesis of the study are based on the AOR. Adjustments for a-priori confounders (age at assessment (21) and socioeconomic status (22)) were made to the model by including these variables to the model as covariates. To address the second aim of the study, separate regression models were constructed to compare the amputation injury subgroup to the uninjured group, the non-amputation injury subgroup to the uninjured group and the amputation subgroup to the non-amputation injury subgroup.

Officers were excluded from the adjusted analyses due to small numbers of poor mental health outcomes in this group (range *n*=1 to *n*=9). Due to the small number of poor mental health outcomes in the amputation injury group (range *n*=16 to *n*=25), bootstrapping using 1000 replications was used and bias-corrected 95% confidence intervals are reported.

Results

579 injured participants and 566 uninjured participants were recruited for the ADVANCE study. The response rate, adjusted for deaths and potential participants with no available contact details, was 59·6% for the injured group and 56·3% for the comparison group. 55·1% of eligible participants with a 'Very Serious Injury' or 'Serious Injury' NOTICAS classification and 62·3% of eligible injured amputee took part in the ADVANCE study. For the purposes of this analysis, one participant was excluded from the uninjured comparison group due to experiencing significant injuries outside of military service, leaving a total of 565 uninjured participants.

Chapter 3 Table 1 shows the sampling characteristics, current sociodemographic and health characteristics of the study participants. 95·2% (*n*=1090/1145) were serving regular/full time reserve service and 4·8% (*n*=55/1145) were reservists at time of sampled deployment. The median number of Afghanistan deployments per participant was 2 (IQR 1, 2). Participants were assessed for the ADVANCE study a median of 8 years (IQR 7, 9) after their sampled deployment. Differences were noted in distribution of rank, with a greater proportion of higher ranks among the uninjured group compared to the injured group, and age, with the uninjured group being slightly older by approximately one year on average compared to the injured group.

The median NISS score for the injured group was 13 (IQR 5, 30). 47·3% (*n*=291/579) were above the suggested cut off of likely mortality from major trauma at point of their aeromedical causality evacuation (NISS≥13).

Body region and mechanisms of injury, stratified by amputation injury status, can be found in Chapter 3 Supplementary Materials 2. 76·3% (*n*=442/579) of injured participants experienced injuries because of blasts, 23·3% (*n*=135/579) by gunshot wounds and 1·2% (*n*=7/579) through other incidents (e.g. vehicular accidents or falls). Participants could sustain multiple injury types, e.g. gunshot wound and explosion injuries. 27·8% (*n*=161/579) of the injured participants sustained at least one limb amputation and 13.1% (*n*=76/579) had ≥2 limb amputations. The top three areas of injury for the amputation injury subgroup include lower limb (98·1% *n*=158/161), head (49·7%, *n*=80/161) and torso (47·2%, *n*=76/161). The top three areas of injury for the non-amputation injury subgroup include lower limb (61·7% *n*=258/418), upper limb (49·8% *n*=208/418) and head (45·0%, *n*=188/418).

Chapter 3 Table 2 reports the rates of mental health outcomes stratified by injury status. 92·2% of participants who reported PTSD also reported either comorbid depression, anxiety or both (mental health multimorbidity). Differences in the distribution of cases of all mental health outcomes between the injured and uninjured groups were noted, with higher rates seen in the injured group compared to the uninjured group on all outcome measures.

Chapter 3 Table 3 displays the unadjusted and adjusted odds ratios for probable PTSD, CMD and mental health multimorbidity, comparing the overall injured group to the uninjured group to address the primary hypothesis. The odds of reporting probable PTSD, depression, anxiety and mental health multimorbidity were greater in the overall injured group compared to the uninjured group, with odds ratios ranging from 1·46 to 1·67. For the analysis on the sample with no bootstrap analysis, please see Chapter 3 Supplementary Materials 3.

The amputation injury subgroup and non-amputation injury subgroups were compared to the uninjured group and also to one another to address the second aim of the study (Chapter 3 Table 3). We observed minimal differences in the odds of reporting any poor mental health outcome between the amputation injury subgroup and the uninjured group, with odds ratios ranging from 0·77 to 0·97. The odds of reporting any poor mental health outcome were lower in the amputation injury subgroup compared to the non-amputation injury subgroup, with odds ratios ranging from 0·38 to 0·52. The odds of reporting any poor mental health outcome were greater in the non-amputation injury group compared to the uninjured group, with odds ratios ranging from 1·74 to 2·01.

CHAPTER 3 TABLE 1: SOCIODEMOGRAPHIC AND DEPLOYMENT CHARACTERISTICS OVERALL AND BY INJURY STATUS, N (%) AND MEDIAN (IQR) ARE PRESENTED

	Total cohort (*n*=1144)	**Uninjured group (*n*=565)**	**Injured group (*n*=579)**	**Amputation injury subgroup (*n*=161)**	**Non-amputation injury subgroup (*n*=418)**
Age at sampled deployment in years, Median (IQR)	25 (22, 29)	26 (23, 29)	25 (22, 29)	25 (22, 28)	25 (22, 29)
Age at assessment in years, Median (IQR)	33 (30, 37)	34 (30, 37)	33 (30, 37)	32 (30, 36)	33 (30, 38)
Serving status at assessment n (%)					
Left Service n (%)	520 (47·6)	99 (17·8)	421 (73·0)	144 (89·7)	277 (67·2)
Ethnicity n (%)					
White	1036 (90·3)	512 (90·4)	524 (90·3)	148 (91·6)	376 (89·8)
All other ethnic groups	108 (9.7)	53 (9·6)	55 (9·7)	13 (8·4)	42 (10·2)
Rank at sampled deployment n (%)					
Lower rank	753 (72·0)	339 (66·5)	413 (76·6)	128 (84·2)	286 (74·0)
Mid rank	253 (20·6)	147 (24·7)	106 (17·1)	20 (10·9)	86 (19·3)
Officer rank	138 (7·4)	79 (8·8)	60 (6·3)	13 (4·9)	47 (6·7)
Weighted percentages are presented along with unweighted cell counts.					

CHAPTER 3 TABLE 2: MENTAL HEALTH OUTCOMES BY INJURY STATUS, N (%, 95% CI)

Mental health outcomes	**Total group** **n (%; *95%CI*)**	**Uninjured group** **n (%; *95%CI*)**	**Injured group** **n (%; *95%CI*)**	**Amputation injury subgroup** **n (%; *95%CI*)**	**Non-amputation injury subgroup** **n (%; *95%CI*)**
PTSD (PCL-C ≥50)	142 (13.9; 11.9, 16.2)	53 (10·5; *8·1, 13·5*)	89 (16·9; *13·9, 20·4*)	15 (9.9; *6·0, 16·0*)	74 (19·3; *15·6, 23·7*)
Depression (PHQ9 ≥10)	216 (20.5; 18.1, 23.1)	87 (16·8; *13·8, 20·4*)	129 (23·6; *20·1, 27·4*)	25 (16·1; *11·0, 23·0*)	104 (26·1 *21·9, 30·8*)
Anxiety (GAD7 ≥10)	182 (17.4; 15.2, 19.9)	71 (13·5; *10·8, 16·8*)	111 (20·8; *17·5, 24·5*)	21 (14·1; *9·3, 20·8*)	90 (23·1; *19·1, 27·6*)
Mental health multimorbidity (caseness on PCL-C & PHQ9 or GAD7)	130 (12.8; 10.8, 15.0)	49 (9·8; *7·4, 12·8*)	81 (15·3; *12·4, 18·7*)	12 (8·2; *4·7, 14·1*)	69 (17·8; *14·2, 22·0*)

Weighted percentages are presented along with unweighted cell counts.

CHAPTER 3 TABLE 3: ODDS RATIOS AND ADJUSTED ODDS RATIOS FROM LOGISTIC REGRESSION OF MENTAL HEALTH OUTCOMES BY INJURY STATUS

Mental health outcome	OR (95% Bias corrected CI)	AOR* (95% Bias corrected CI)
Injury status: Injured-Overall *(ref: uninjured)*		
PTSD (PCL-C ≥50)	1·77 (1·28, 2·67)	1·67 (1·16, 2·41)
Depression (PHQ9 ≥10)	1·58 (1·18, 2·16)	1·46 (1·08, 2·03)
Anxiety (GAD7 ≥10)	1·65 (1·22, 2·30)	1·56 (1·13, 2·24)
Mental health multimorbidity (caseness on PCL & PHQ9 or GAD7)	1·71 (1·18, 2·65)	1·62 (1·12, 2·49)
Injury status: Injured-Amputation subgroup *(ref: uninjured)*		
PTSD (PCL-C ≥50)	1·00 (0·48, 1·68)	0·92 (0·47, 1·70)
Depression (PHQ9 ≥10)	1·02 (0·62, 1·66)	0·87 (0·48, 1·38)
Anxiety (GAD7 ≥10)	1·05 (0·55, 1·74)	0·97 (0·53, 1·64)
Mental health multimorbidity (caseness on PCL & PHQ9 or GAD7)	0·85 (0·40, 1·61)	0·77 (0·36, 1·45)
Injury status: Injured-Non-amputation injury subgroup *(ref: uninjured)*		
PTSD (PCL-C ≥50)	2·00 (1·44, 3·13)	2·01 (1·32, 2·89)
Depression (PHQ9 ≥10)	1·82 (1·27, 2·45)	1·74 (1·24, 2·38)
Anxiety (GAD7 ≥10)	1·91 (1·39, 2·71)	1·83 (1·27, 2·59)
Mental health multimorbidity (caseness on PCL & PHQ9 or GAD7)	2·08 (1·43, 3·17)	2·00 (1·41, 3·07)
Injury status: Injured-Amputation subgroup *(ref: non-amputation injury subgroup)*		
PTSD (PCL-C ≥50)	0·48 (0·25, 0·85)	0·45 (0·23, 0·87)
Depression (PHQ9 ≥10)	0·56 (0·36, 0·92)	0·49 (0·26, 0·76)
Anxiety (GAD7 ≥10)	0·55 (0·31, 0·91)	0·52 (0·29, 0·87)

Mental health outcome	**OR (95% Bias corrected CI)**	**AOR* (95% Bias corrected CI)**
Mental health multimorbidity (caseness on PCL & PHQ9 or GAD7)	0·41 (0·19, 0·74)	0·38 (0·18, 0·70)

*Adjusted for socioeconomic status and age. Officers excluded.

Analysis in this table was bootstrapped with *n*=1000 replicates.

Discussion

This study hypothesised that rates of probable PTSD and common mental disorders would be greater amongst those who sustained physical injuries in Afghanistan compared to physically uninjured UK military personnel who had also deployed to Afghanistan. Overall, sustaining a combat injury was associated with between a 46-67% increase in odds of reporting PTSD, depression and anxiety symptoms compared to uninjured personnel. Planned subgroup analysis identified these differences were driven mostly by those with non-amputation related injuries, and that amputees had no differences in the odds of reporting probable PTSD, anxiety or depression compared to uninjured personnel and significantly lower odds of reporting poor mental health outcomes compared to their non-amputation related injured peers.

Studies of US military personnel report that the rates of PTSD vary from 4·2% to 58·9% and depression from 3·0% to 38·3% amongst those physically injured in combat (23-26). Data available on UK combat-injured personnel suggested rates of probable PTSD of 18·5% and common mental disorders of 28·2% for those medically evacuated from Iraq/Afghanistan with a physical injury (2), though these data were relating to outcomes in the short term (median time since deployment of 2 years (IQR 0.8, 4.5)). The ADVANCE study data reports similar rates of mental ill health at median time since deployment of 8 years (IQR 7, 9), suggesting that the increased risk of poor mental health outcomes among combat-injured personnel persists over the short to longer term.

Previous research has presented mixed results regarding combat amputation injury and mental health outcomes. One study comparing a combat amputation injury group to a serious extremity non-amputation injury group found that amputees were significantly less likely to report PTSD, but significantly more likely to report mood disorders (10). In the ADVANCE study, amputees reported no significant differences in mental health outcomes compared to our uninjured group, and significantly lower rates compared to non-amputation injured personnel Whilst both injured amputees and injured non-amputees received Defence Medical Service rehabilitation to return them to the highest level of function achievable, it is possible our injured amputee group had access to additional services or resources to help with mental health difficulties. Indeed, access to therapeutic services, either psychological or related to psychiatric medication, is worthy of further investigation. It remains to be seen whether increasing age, possible deterioration in mobility and other factors including possible age-related pain might be associated with worsening mental health outcomes in this cohort.

Studies investigating the media representation of combat-injury have noted that, in comparison to injuries not sustained in a 'combat' scenario, combat injuries have an associated greater positive worth amongst media and the UK population, often being defined as 'heroic' (27). There is minimal research investigating a possible hierarchy of type of combat injuries. Amputation is perceived as a "signature injury" from the British involvement in the Iraq and Afghanistan conflicts and is an easily visible injury. Events such as the INVICTUS games, a multi-national Olympic-style sporting event for injured servicemen/women, have also put these injuries front and centre of public perception. It is possible that such praise and perception has a positive impact on mental health (28). Those with injuries that do not allow them to engage in such activities or perhaps are less obvious, such as those with significant pain, might not benefit from such praise and attention, which may account for the increased likelihood of reporting poor mental health outcomes in our cohort. Further investigation into hierarchy of wounding within those who sustained combat injuries is recommended.

This study has implications for clinical practice. Both civilian and military clinicians should be encouraged to routinely enquire about mental health in their serving and veteran patients who have served in conflicts such as Afghanistan and Iraq. Patients do not have to present with obvious injuries to experience poor mental health outcomes. Stigma around mental health in the military might discourage patients from seeking help (29). It is also of note that whilst amputees appeared to have similar mental health outcomes compared to our uninjured group, both injured and uninjured groups reported greater rates of PTSD compared to the general population estimates from national surveys such as the Adult Psychiatric Morbidity Survey (17). Additionally, over 90% of both the uninjured and injured groups with PTSD had comorbid depression or anxiety (mental health multimorbidity). The psychological burden of comorbid PTSD and depression has been found to be considerably greater than that of PTSD or depression alone (19) and is associated with poorer quality of life and increased suicidality. Injured personnel without amputation were significantly more likely to report mental health multimorbidity compared to both the uninjured cohort and the amputation injury subgroup. The psychological burden of these non-amputation related injuries is worthy of further investigation, along with other notable comorbidities such as mild-/traumatic brain injury, pain and PTSD (often labelled together as the polytrauma clinical triad) (30).

Of the total number of UK Armed Forces personnel injured in Afghanistan who met our study criteria, over 55% of those with a Very/-Serious Injury NOTICAS classification took part in the ADVANCE study. Great lengths were taken to have a comparison group as similar to the injured

group as possible based on age, rank, role on deployment, regiment and deployment era. Weighting based on differences between responders and non-responders was also implemented. Participants of the ADVANCE study complete a comprehensive health assessment using validated health measures.

To attempt to ensure the study was accessible to participants with a range of difficulties, accommodation was provided and travel expenses were paid. Attempts were made to include participants who had left the military, including investigating electoral roll data, working with charities and social media recruitment. For those in service, participants were invited in person from unit visits as well as via email and postal invitations. Despite these efforts, it is still possible that the hardest to reach or those who declined to take part, both in the uninjured and injured groups, might represent a group with worse physical or mental health, and is a potential limitation of the study.

Another limitation of this study is the use of the PCL-C, which lists only DSM-IV symptoms of PTSD. Future follow-up appointments for the ADVANCE study will use the PCL-5, which assesses the DSM-V symptoms of PTSD. Mild-/traumatic brain injury was also not investigated. Future follow-up appointments for the ADVANCE study will implement the Ohio-State Traumatic Brain Injury Screener questionnaire (31) to address this limitation. This screener includes information on loss of consciousness (including length of time unconscious) as well as symptoms such as dizziness and memory loss. Mediation analysis was beyond the scope of this current paper, however mediating factors such as current/chronic pain, psychiatric medication use and access to therapeutic services will be explored within the ADVANCE study cohort in the future.

Adverse mental health outcomes were more prevalent amongst injured UK military personnel compared to our uninjured comparison group. However, mental health outcomes appear to vary depending on the type of injury sustained, with those who experienced non-amputation related injuries having greater odds of poor mental health outcomes compared to those who sustain amputation injuries. This study also emphasises the potential psychological burden of multiple mental health problems amongst both injured and uninjured groups. Long term follow-up conducted by the ADVANCE study over the next twenty years of this cohort will give us insight into some of the reasons for the different mental health outcomes between these groups, and observe whether they are maintained with reduced mobility, age-related pain or other factors associated with increased age.

Data Sharing Statement

Data are available upon reasonable request. Given the sensitive nature of the participants, the data have not been made widely available. Requests for data will be considered on a case-by-case basis and subject to UK Ministry of Defence clearance. The study protocol is available for researchers open access (11).

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Role of Funder

The funders had no direct role in interpretation of results or decision to submit for publication. No money has been received by pharmaceutical or any other agency to write this article.

Contributors

Daniel Dyball: Completed literature search; visualisation (designed figure); investigation (data collection); data curation; formal analysis; data interpretation and writing (original draft and editing).

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

Susie Schofield: Formal analysis; writing (review).

Paul Cullinan: Funding acquisition; methodology; writing (review).

Christopher J Boos: Conceptualisation; funding acquisition; methodology; writing (review).

Anthony MJ Bull: Funding acquisition; methodology; writing (review).

Simon Wessely: Funding acquisition: conceptualisation: writing (review).

Sharon AM Stevelink: Supervision; writing (review).

Nicola T Fear: Funding acquisition; methodology; supervision; writing (review).

Both Daniel Dyball and Susie Schofield have verified the underlying data reported in this manuscript.

Key messages

Evidence before this study:

- Rates of PTSD (4%-58%), and depression (3%-38%) have been observed in samples of combat injured personnel, but most research compares rates of subtypes of injury (e.g. those who sustained gastrointestinal injuries compared to those who sustained non-gastrointestinal injuries) rather than a suitable uninjured comparison group.

Evidence from this study:

- Sustaining a combat injury while on deployment in Afghanistan was associated with greater odds of reporting anxiety, depression, PTSD and mental health multimorbidity compared to the uninjured comparison group.
- Analysis by subtypes of injury (amputation and non-amputation injury) indicated that sustaining an amputation injury was not associated with any significant differences in the odds of reporting anxiety, depression, PTSD or mental health multimorbidity compared to the uninjured group. Those who sustained non-amputation injuries had significantly greater odds of reporting anxiety, depression, PTSD or mental health multimorbidity compared to the uninjured group and amputation injured subgroup.

Strengths of this study:

- The study benefits from a relatively large sample size and a frequency matched uninjured comparison group. More precise confidence intervals were also generated from bootstrapping analysis.

Limitations of the study:

- The use of the PCL-C, a DSM-IV based measure of PTSD. This means that the definition of PTSD used, whilst mostly similar, is historic compared to the current DSM-V version.
- A response bias may exist due to the possibility that injured personnel with worse health, either physical or mental, might be less willing or less able to attend a full study day at the Defence Medical Rehabilitation Centre.
- Assessing mediating factors, such as pain, psychiatric medication use or access to therapeutic services, were beyond the scope of the current analysis.

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Post-Traumatic Growth amongst UK Armed Forces personnel who deployed to Afghanistan and the role of combat injury, mental health and pain
"Post-traumatic growth is more than just the absence of mental illness."

Overview

In this chapter, I will attempt to answers aims 2.1-2.3 by exploring the relationship between combat injury and Post-Traumatic Growth (PTG). The chapter will first report on the rates of tertiled overall scores on the DPTGI (no/a low degree of PTG, a moderate degree of PTG and a large degree of PTG) between the overall injured group, the uninjured group, the amputation injury subgroup and the non-amputation injury subgroup. The chapter then goes on to describe whether depression, PTSD and pain mediate the relationship between combat injury and post-traumatic growth. This chapter also discusses potential reasons for the discrepancies in rates of PTG between those who sustained an amputation injury and those who sustained a non-amputation injury, the potential reason why pain mediates PTG and the clinical implications for this study.

Aim 2.1 Investigate PTG experienced as a result of deployment to Iraq/Afghanistan between injured and uninjured groups of Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).

Aim 2.2 Investigate whether subgroups of the injured group, specifically those who sustained an amputation injury and non-amputation injury, exhibit differences in rates of deployment related PTG.

Aim 2.3 Investigate whether depression, PTSD and pain mediate the relationship between combat injury and PTG.

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Post-Traumatic Growth amongst UK Armed Forces personnel who deployed to Afghanistan and the role of combat injury, mental health and pain: The ADVANCE cohort study

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Conflict of interest

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Keywords: Afghanistan; military personnel; wound and injuries; Post-traumatic growth

Word count

3932

Abstract

Background: Post-Traumatic Growth (PTG) is a positive psychological consequence of trauma. The aims of this study were to investigate whether combat injury was associated with deployment-related PTG in a cohort of UK military personnel who deployed to Afghanistan, and whether Post-Traumatic Stress Disorder (PTSD), depression and pain mediate this relationship.

Methods: 521 physically injured (*n*=138 amputation; *n*=383 non-amputation injury) and 514 frequency-matched uninjured personnel completed questionnaires including the deployment-related Post-Traumatic Growth Inventory (DPTGI). DPTGI scores were categorised into tertiles of: no/ low (score 0-20), moderate (score 21-34) or a large (35-63) degree of deployment-related PTG. Analysis was completed using generalised structural equation modelling.

Results: A large degree of PTG was reported by 28.0% (*n*=140) of the uninjured group, 36.9% (*n*=196) of the overall injured group, 45.4% (*n*=62) of amputee and 34.1% (*n*=134) of the non-amputee injured subgroups. Combat injury had a direct effect on reporting a large degree of PTG (Relative Risk Ratio (RRR) 1.59 (95% Confidence Interval (CI) 1.17, 2.17)) compared to sustaining no injury. Amputation injuries also had a significant direct effect (RRR 2.18 (95% CI 1.24, 3.75)), but non-amputation injuries did not (RRR 1.35 (95% CI 0.92, 1.93)). PTSD, depression and pain partially mediate this relationship, though mediation differed depending on injury subtype. PTSD had a curvilinear relationship with PTG, whilst depression had a negative association and pain had a positive association.

Conclusions: Combat injury, in particular injury resulting in traumatic amputation, is associated with reporting a large degree of PTG.

Introduction

Armed Forces personnel who were deployed to the Middle East during the conflicts in Iraq and Afghanistan have been the subject of much research over the past two decades. While the negative psychological consequences of such deployments have been well researched (1-3), the research on positive psychological outcomes has been limited. Post-Traumatic Growth (PTG) is one such potential positive outcome, being the experience of beneficial psychological change following exposure to trauma (4). To the authors best knowledge, only two papers have investigated PTG in the UK Armed Forces. The first establishes that PTG can be elicited during therapy for PTSD (5). The second paper investigates PTG amongst Iraq/Afghanistan deployed UK personnel and establishes that those who reported deployment-related PTG also reported better overall health, better mental health (excluding PTSD) and deployment-related factors such as belief that they may be seriously injured or killed or a reporting a greater number of combat experiences (6), though there are mixed results on the effect of combat experiences in the US literature (7, 8). The UK analysis (6) investigated overall health, but not physical injuries received during deployment and their potential effect on PTG. Data on the US military has found support for the experience of PTG amongst combat-injured amputees (9).

It is well recognised that PTG can occur after both physical or psychological trauma (10), and it has been shown to be associated with better mental health outcomes such as lower rates of depressive disorders in longitudinal studies of those with serious medical conditions, (11). One significant exception to this is PTSD, which has an inverted ‘u’-shaped (curvilinear) relationship with PTG (12), whereby as PTSD symptoms increase, so does PTG, until a threshold is met, at which point as PTSD symptoms increase, PTG decreases. Health related quality of life, such as levels of pain/discomfort, have also been found to be better (e.g. lower levels of pain/discomfort) amongst those who experience greater PTG (11). Sustaining a physical combat injury is associated with greater rates of PTSD, depression and pain in both US and UK Armed Forces (13-15), but is also associated with high rates of PTG (9, 16). No known studies have investigated whether PTSD, depression and pain mediate the relationship between physical combat injury and PTG.

The ADVANCE study follows a cohort of UK Armed Forces personnel who sustained a physical combat injury in Afghanistan and an uninjured comparison group (17). Its aim is to investigate the impact of sustaining a physical combat injury on long-term health. We have recently reported that overall, those who were injured were more likely to report poor mental

health outcomes including PTSD, depression, anxiety, and mental health multimorbidity, however this varied by the type of injury sustained (13). Those with non-amputation injuries were more likely to report poor mental health outcomes compared to the uninjured comparison group. However, those with amputation-related injuries were no more likely to report poor mental health outcomes than the uninjured group and were less likely to report poor mental health outcomes when compared to the non-amputation related injury group.

In this paper, we aim to: 1) report on PTG experienced as a result of military deployments to Iraq/Afghanistan in a cohort of physically injured and a frequency-matched uninjured comparison group of UK Armed Forces personnel (the ADVANCE study cohort), 2) examine whether those with amputation injuries and those with non-amputation injuries differ in likelihood of reporting deployment-related PTG compared to the uninjured group and 3) examine whether differences in PTG are mediated by pain, PTSD symptoms and depression.

Methods

Participants/Procedure

Injured participants were recruited from a sample of physically combat-injured UK Armed Forces personnel, provided by the Ministry of Defence (MoD) Defence Statistics (Health) (17). Between 2015 and 2020, 579 physically injured UK Armed Forces men who deployed to Afghanistan and were aero-medically evacuated to a UK hospital were recruited into the ADVANCE study. A further 566 UK Armed Forces personnel, who were recruited from a recruitment sample frequency-matched to the injured group based on sex, age, rank, role on deployment, regiment and period of deployment (deployed to Afghanistan during the same time period, e.g. HERRICK 4, April 2006-September 2006). Participants completed a study day (hereby defined as the ADVANCE assessment) consisting of a comprehensive health investigation, a research nurse-led clinical interview and self-completed questionnaire. Response rates adjusted for deaths and participants with no contact details were 59.6% for the injured group and 56.3% for the uninjured comparison group (13). A measure of PTG was introduced to the ADVANCE cohort in 2018. From this point, participants completed the questionnaire as part of their clinical assessments. All participants who attended their ADVANCE study appointment prior to this date were invited to complete the questionnaire either online or via post.

Materials

PTG

The Post-Traumatic Growth Inventory is a 21-item measure of PTG (4), of which a deployment -related version (DPTGI) was administered to our participants (6). The stem question for the DPTGI was “Please read each statement and tell us whether you have changed for the better as a result of ALL your deployments to Iraq/Afghanistan since 2002”. Scores range from 0-63, with higher scores indicating greater PTG.

COMBAT INJURY

Initial information on combat injury was collected from MoD medical records, with additional details provided by self-report in the clinical interview, including type of injury (e.g. amputation). Amputees were defined as any amputation above/below/through the knee or above/below the elbow. Participants who experienced a partial amputation only (e.g. digit, partial hand, partial foot) were included in the non-amputation injury subgroup.

DEPRESSION

Depression was measured using the Patient Health Questionnaire-9 (PHQ), a nine-item measure of depression. Probable depressive disorder was defined as a score of ≥10 (scores range from 0-27) (18).

PAIN

Pain was evaluated using the EQ-5D-5L quality of life measure, a six-item self-report questionnaire that identifies mobility, self-care, usual-activities, pain/discomfort, mental health and overall health (19). The pain subscale score was used and a score of ≥2 was used to indicate current moderate-extreme pain (scores range from 0-4). This subscale has been established to have moderate-strong correlation with other pain measures (20).

PTSD

PTSD was measured using the PTSD Check List (PCL-C), a 17-item measure of PTSD according to the DSM-IV-related symptoms over the past month. Probable PTSD was defined as a score of ≥50 (scores range from 17-85) (21).

TIME SINCE DEPLOYMENT

Time since deployment was measured as the number of years between their age at sampled deployment/injury to age at completion of the DPTGI measure.

Ethics

The ADVANCE Study has full ethical approval from the UK Ministry of Defence Research Ethics Committee (MODREC; protocol No:357/PPE/12).

Data analysis

Data analysis was performed using STATA version 17.0. Cronbach's alpha was used to assess internal consistency of the DPTGI. Scores of the DPTGI were converted to tertiles based on the full sample, creating three categories: No/a low degree of PTG (scores 0-20), a moderate degree of PTG (scores 21-34) and a large degree of PTG (35-63). Rank was coded into three categories as an indicator of socioeconomic status; NATO OR2-OR4 (lower rank), NATO OR5-OR9 (mid rank) and NATO OF1-OF6 (officer rank) (22).

Socioeconomic status/rank (6), age (6) and time since sampled deployment (23) were controlled for due to the strong evidence base for these associations with PTG. The injured group was investigated as a whole, and then split into the two subgroups from which the initial sampling was based; those with amputation injuries and those with non-amputation injuries (17).

Weighted percentages are presented along with unweighted cell counts based on sampling and response characteristics of those recruited into the ADVANCE study. Sampling weights were applied to the injured group, which accounted for the under-sampling of those with less-severe injuries defined by NOTICAS causality rating (17). Response weights were calculated based on age, rank and branch of service at time of sampling due to more officers, royal marines and older (by approximately one year) participants being represented in those that took part in the study. Response weights and sampling weights were multiplied together and applied to descriptive tables using the 'svy' command in STATA. Response bias to completing the DPTGI between the uninjured, injured, amputation injury subgroup and non-amputation injury subgroup was assessed via χ^2.

Due to the known curvilinear relationship between PTSD and PTG (12), the PCL-C score was centred (PCL-C score-mean score) and a second variable (centred PCL-C score^2) was included as confirmed by a linear regression and subsequent likelihood ratio test. Participants with >3 items missing from the DPTGI were excluded (n=2). 400 participants did not complete one item of the DPTGI due to an administration error. Missing data for participants with ≤3 items missing on an item-level on the DPTGI were imputed using two-way imputation (n=434) (24). Multiple imputation was considered, however missing data on any other variable of interest was low (<1%; n=8), and so was dealt with using casewise deletion. Generalised Structural Equation Modelling (GSEM) models using imputed and unimputed scores were compared and no notable differences between the GSEM models were observed (available from the authors).

GSEM multinomial models were used in three steps. The first model that assessed the relationship between PTSD, PTSD^2, depression and pain with a moderate and a large degree of PTG compared to no/a low degree of PTG. The second investigated whether, when compared to the uninjured group, the overall combat injured group, the amputation injury subgroup and the non-amputation injury subgroup were associated with a moderate or a large degree of PTG compared to no/a low degree of PTG (unmediated models). The third step was to introduce variables which assessed whether PTSD, PTSD^2, depression and pain mediated these relationships (mediated models). All continuous variables were standardised prior to input into the model using the 'zval' command. Coefficients are reported in the GSEM figures, and exponentiated coefficients (Relative Risk Ratios (RRR)) are reported in tables and text for direct and indirect effects of injury status on PTG. Bias-corrected confidence intervals are presented and were bootstrapped using 1000 reps. Direct and indirect effects

were estimated using non-linear combinations of estimators (the 'nlcom' command). Due to inconsistent mediation, total effects were not reported.

Results

90.4% (*n*=1035/1145) of the ADVANCE study participants completed the DPTGI. 90.0% (*n*=521/579) of the overall injured group, 85.0% (*n*=138/162) of the amputation subgroup and 91.6% (*n*=383/418) of the non-amputation injury subgroup completed the DPTGI. 90.8% (*n*=514/566) of the uninjured group completed the DPTGI. No significant differences were noted between the rates of injured amputees, injured non-amputees and uninjured participants who completed the DPTGI, (χ^2 (df=3) 1.77, *p*=0.17). 27.0% (*n*=279) of the sample completed the DPTGI ≥12 months after their ADVANCE assessment.

Chapter 4 Table 1 describes the sociodemographic, deployment-related factors and frequency of the DPTGI tertiles by injury status. Cronbach's alpha for the DPTGI was 0.94, suggesting excellent internal consistency. The overall median score on the DPGTI was 28 (IQR 16, 39). Amongst the uninjured group, the median DPTGI score was 26 (IQR 15, 36) and amongst the injured group the median DPTGI score was 30 (IQR 17, 42). The amputation subgroup median score was 33 (IQR 21, 46) and the non-amputation related injury subgroup median score was 28 (IQR 16, 41). The uninjured group were approximately one year older on average, had a greater proportion of higher ranks, deployed more recently to their sampled deployment era by approximately six months on average, reported lower PTSD and depression scores, reported less pain and had a lower proportion of low scores on the DPTGI compared to the injured group.

Chapter 4 Figure 1 shows the GSEM applied to the whole cohort, with a moderate or large degree of PTG (both compared to no/a low degree of PTG) as the dependent variable and PTSD symptoms, PTSD symptoms^2, depression symptoms and reporting moderate-extreme pain at ADVANCE assessment as independent variables after adjusting for confounders. PTSD symptoms had moderate-strong positive associations with reporting both a moderate and large degree of PTG compared to reporting no/a low degree of PTG. PTSD symptoms^2 and depression symptoms had moderate-very strong negative associations with reporting a moderate degree and a large degree of PTG compared to no/a low degree of PTG. Pain had no/very minimal associations with reporting a moderate degree of PTG, but had a moderate positive association with a large degree of PTG compared to no/a low degree of PTG.

Chapter 4 Figure 2 show the GSEM investigating the association between combat injury, amputation injury and non-amputation injury with reporting a large degree of PTG, mediated

by PTSD, depression and pain after adjusting for confounders. Whilst PTSD symptoms, PTSD symptoms^2, depression and pain continued to be associated with reporting a large degree of PTG in the combat injury model (Chapter 4 Figure 2), pain was no longer associated in the amputation (Chapter 4 Figure 3) and non-amputation injury (Chapter 4 Figure 4) subgroups. Similar but smaller effects were noted in the GSEM models for a moderate degree of PTG (Chapter 4 Supplementary Materials 1).

Chapter 4 Table 2 reports on the direct and indirect effects of the GSEM models reported in Chapter 4 Figures 2-4. In the injured group, after adjusting for confounders, sustaining an injury had a direct effect on reporting a large degree of PTG compared to no/a low degree of PTG (RRR 1.59 (95%CI 1.17, 2.17)) and also an indirect effect through PTSD symptoms, depression and pain. No indirect effect was noted for PTSD symptoms^2. Sustaining an amputation injury had a direct effect on reporting a large degree of PTG (RRR 2.37 (95%CI 1.22, 3.51)), but no indirect effects were noted for any of the mediators. Sustaining a non-amputation injury did not have a direct effect on reporting a large degree of PTG (RRR 1.35 (95%CI 0.92, 1.93)), but did have indirect effects through PTSD symptoms and depression. No indirect effect was noted for PTSD symptoms^2 or pain.

CHAPTER 4 TABLE 1: SOCIODEMOGRAPHIC, DEPLOYMENT AND POST-TRAUMATIC GROWTH CHARACTERISTICS BY INJURY STATUS, N (%) AND MEDIAN (IQR)

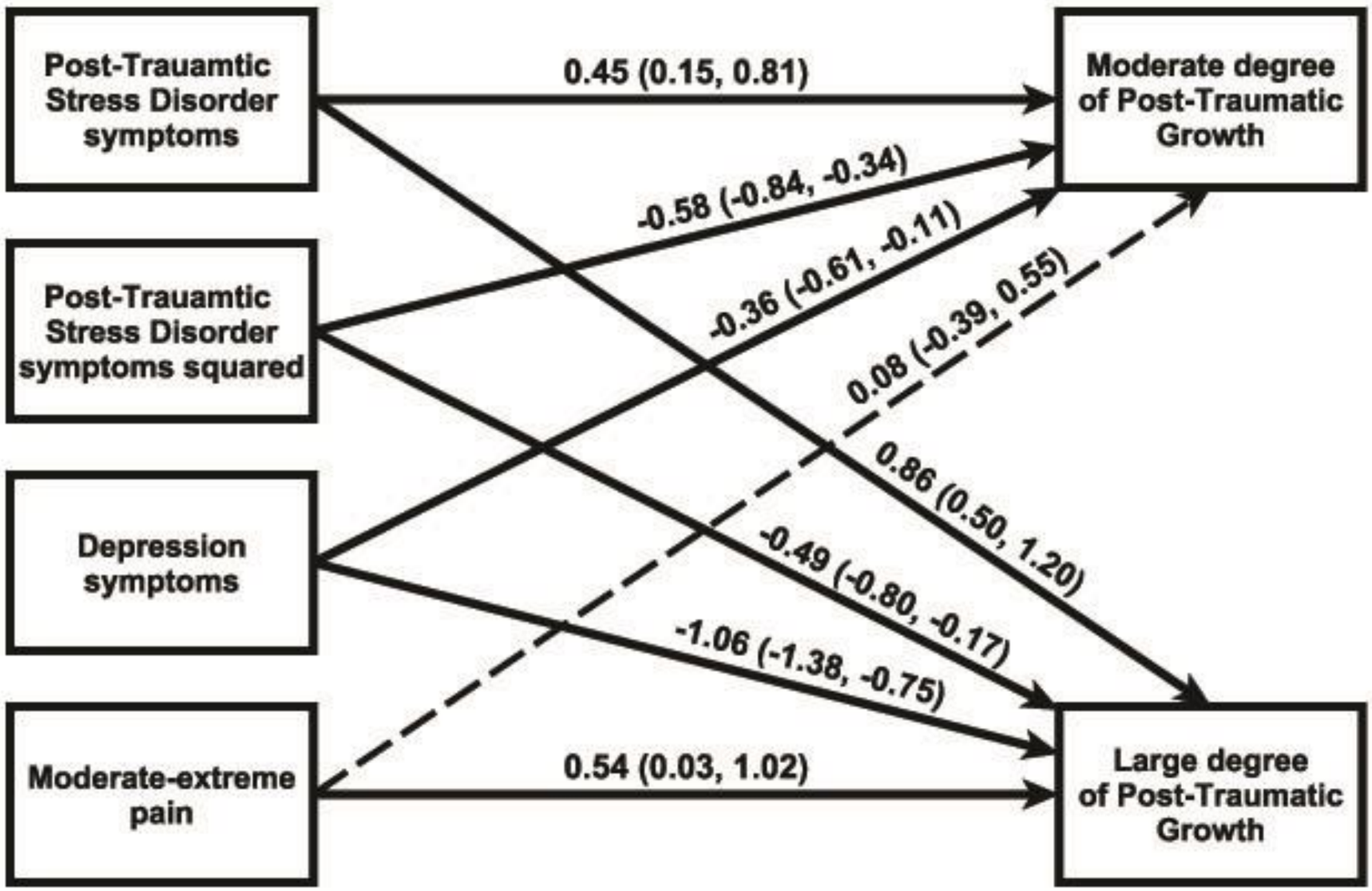
	Total group (*n*=1035)	**Uninjured group (*n*=514)**	**Injured group: Overall (*n*=521)**	**Injured group: Amputation subgroup (*n*=138)**	**Injured group: Non-amputation injury subgroup (*n*=383)**
Median age at ADVANCE assessment (IQR)	34 (30, 37)	34 (31, 37)	33 (30, 37)	32 (30, 36)	34 (30, 38)
Ethnicity *n* (%)					
White Caucasian	939 (90.5)	465 (90.1)	474 (90.8)	127 (92.0)	347 (90.4)
All Other Ethnic Minorities	96 (9.5)	49 (9.9)	47 (9.2)	11 (8.0)	36 (9.6)
Rank at sampling *n* (%)					
Lower rank	670 (70.8)	302 (65.1)	368 (75.7)	111 (84.7)	257 (72.8)
Mid rank	236 (21.4)	138 (25.7)	98 (17.7)	17 (10.9)	81 (20.0)
Officer rank	129 (7.8)	74 (9.2)	55 (6.6)	10 (4.4)	45 (7.2)
Median number of deployments to Iraq/Afghanistan (IQR)	2 (1, 3)	2 (2 ,3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Median years between sampling deployment and DPTGI assessment (IQR)	9.1 (8.0, 10.3)	8.8 (7.8, 10.0)	9.3 (8.2, 10.6)	9.1 (7.9, 9.9)	9.5 (8.3, 10.8)
Median PCL score at ADVANCE assessment (IQR)	26 (19.5, 37)	23 (18, 32)	29 (21, 41)	25 (20, 33)	30 (22, 44)

	Total group (*n*=1035)	**Uninjured group (*n*=514)**	**Injured group: Overall (*n*=521)**	**Injured group: Amputation subgroup (*n*=138)**	**Injured group: Non-amputation injury subgroup (*n*=383)**
Median PHQ9 score at ADVANCE assessment (IQR)	3 (1, 8)	2 (0, 7)	4 (1, 9)	4 (1, 7)	4 (2, 9)
Moderate/severe/extreme pain or discomfort at ADVANCE assessment *n* (%)	184 (18.7)	60 (12.3)	124 (24.0)	27 (20.1)	97 (25.3)
No/a low degree of PTG (DPTGI 0-20)	360 (34.4	197 (37.1)	163 (32.1)	33 (24.4)	130 (34.6)
Moderate degree of PTG (DPTGI 21-34)	339 (32.8)	177 (34.9)	162 (31.0)	43 (30.2)	119 (31.3)
Large degree of PTG (DPTGI 35-63)	336 (32.8)	140 (28.0)	196 (36.9)	62 (45.4)	134 (34.1)

Weighted percentages are presented alongside unweighted cell counts.

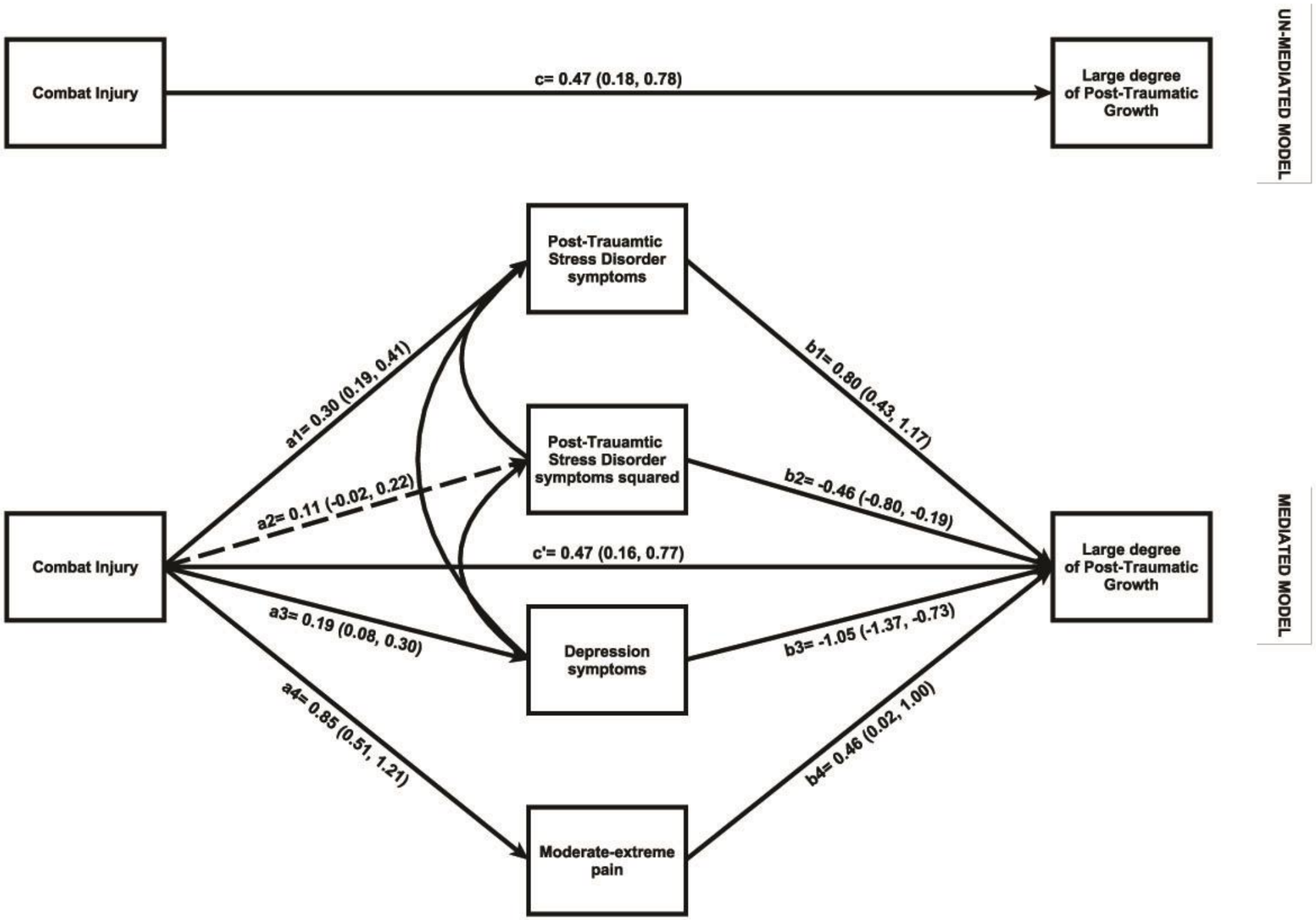
Acronyms: Deployment-related Post-Traumatic Growth Inventory (DPTGI); Inter-Quartile Range (IQR); Multidimensional Scale of Perceived Social Support (MSPSS); Patient Health Questionnaire (PHQ9); Post-Traumatic Growth (PTG); Post-Traumatic Stress Disorder (PTSD); PTSD Check List (PCL)

CHAPTER 4 FIGURE 1: GENERALISED STRUCTURAL EQUATION MODEL INVESTIGATING THE EFFECT OF PTSD, DEPRESSION AND PAIN ON A MODERATE/LARGE DEGREE OF PTG IN THE WHOLE COHORT



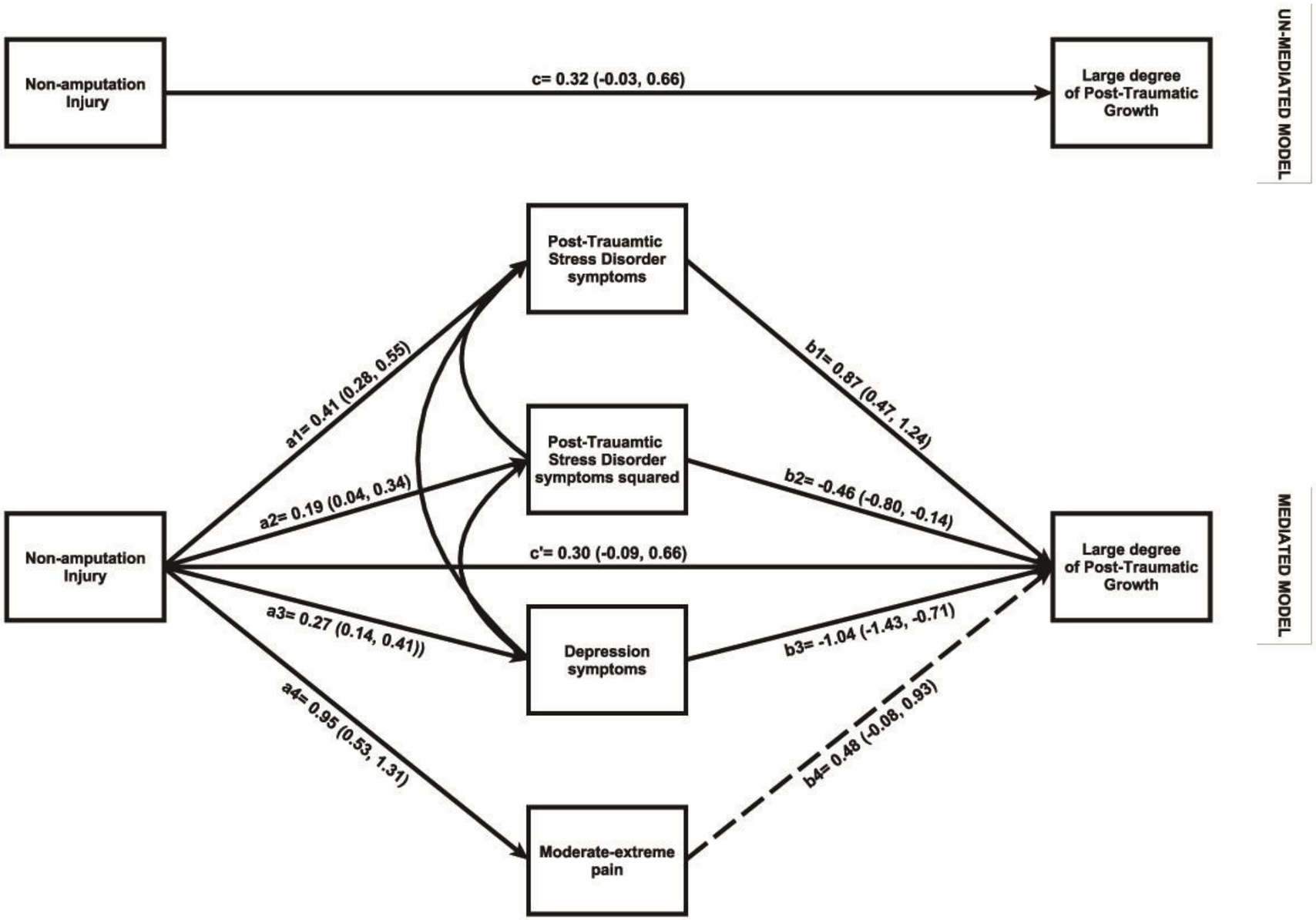
MODEL ADJUSTED FOR AGE AT ADVANCE ASSESSMENT, RANK AT SAMPLING AND TIME SINCE SAMPLED DEPLOYMENT/INJURY TO COMPLETING THE DPTGI. STANDARDISED COEFFICIENTS AND 95% CONFIDENCE INTERVALS SHOWN. CONFIDENCE INTERVALS THAT SUGGEST NON-SIGNIFICANT ASSOCIATIONS ARE DENOTED AS DOTTED LINES.

CHAPTER 4 FIGURE 2: GENERALISED STRUCTURAL EQUATION MODEL ASSESSING THE RELATIONSHIP BETWEEN COMBAT INJURED GROUP (VERSUS UNINJURED GROUP) AND REPORTING A LARGE DEGREE OF PTG, MEDIATED BY PTSD SYMPTOMS, PTSD SYMPTOMS2, DEPRESSION AND PAIN



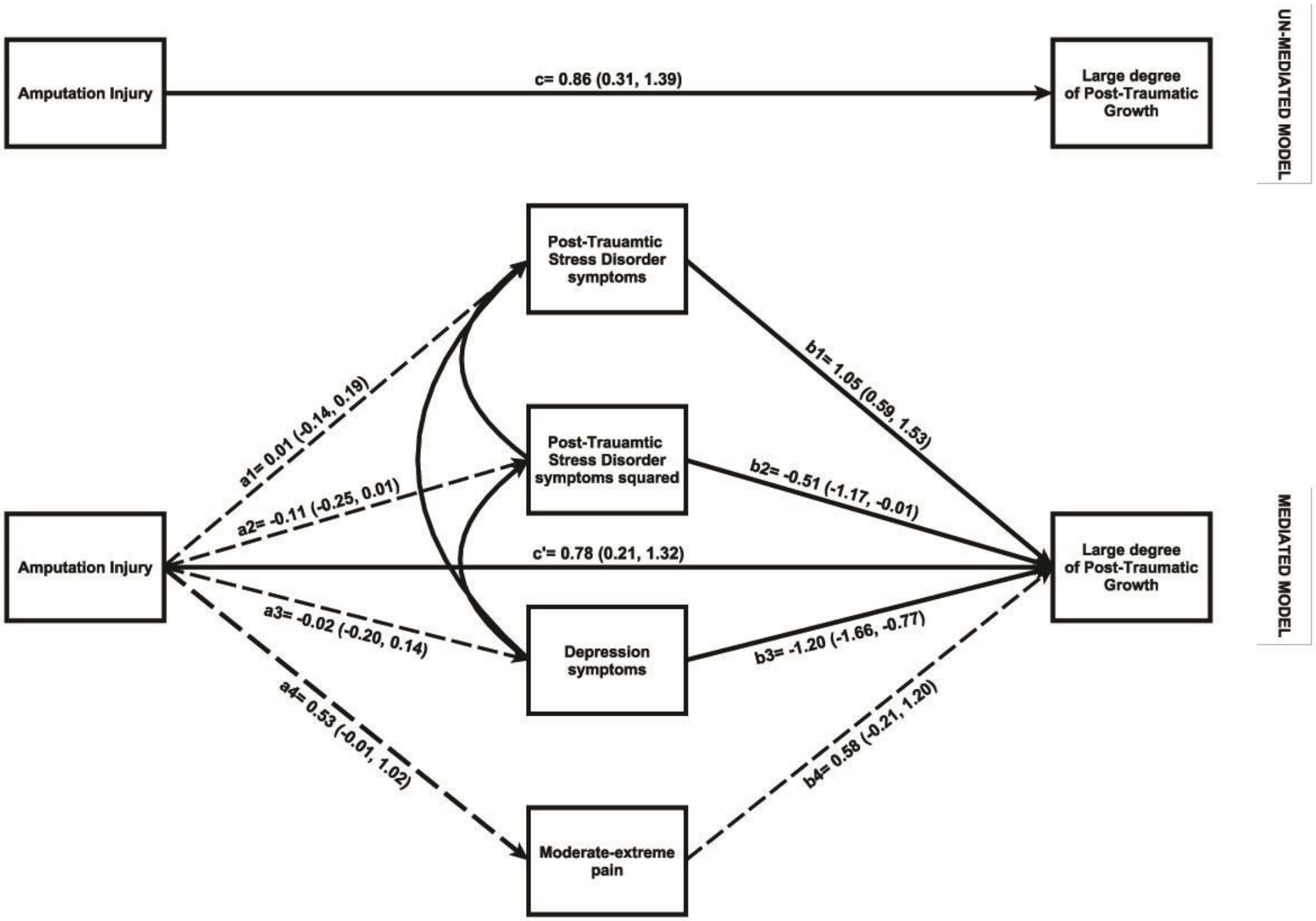
MODEL ADJUSTED FOR AGE AT ADVANCE ASSESSMENT, RANK AT SAMPLING AND TIME SINCE SAMPLED DEPLOYMENT/INJURY TO COMPLETING THE DPTGI. STANDARDISED COEFFICIENTS AND 95% CONFIDENCE INTERVALS SHOWN. CONFIDENCE INTERVALS THAT SUGGEST NON-SIGNIFICANT ASSOCIATIONS ARE DENOTED AS DOTTED LINES.

CHAPTER 4 FIGURE 3: GENERALISED STRUCTURAL EQUATION MODEL ASSESSING THE RELATIONSHIP BETWEEN AMPUTATION INJURED SUBGROUP (VERSUS UNINJURED GROUP) AND REPORTING A LARGE DEGREE OF PTG, MEDIATED BY PTSD SYMPTOMS, PTSD SYMPTOMS2, DEPRESSION AND PAIN



MODEL ADJUSTED FOR AGE AT ADVANCE ASSESSMENT, RANK AT SAMPLING AND TIME SINCE SAMPLED DEPLOYMENT/INJURY TO COMPLETING THE DPTGI. STANDARDISED COEFFICIENTS AND 95% CONFIDENCE INTERVALS SHOWN. CONFIDENCE INTERVALS THAT SUGGEST NON-SIGNIFICANT ASSOCIATIONS ARE DENOTED AS DOTTED LINES.

CHAPTER 4 FIGURE 4:GENERALISED STRUCTURAL EQUATION MODEL ASSESSING THE RELATIONSHIP BETWEEN NON-AMPUTATION INJURED SUBGROUP (VERSUS UNINJURED GROUP) AND REPORTING A LARGE DEGREE OF PTG, MEDIATED BY PTSD SYMPTOMS, PTSD SYMPTOMS2, DEPRESSION AND PAIN



MODEL ADJUSTED FOR AGE AT ADVANCE ASSESSMENT, RANK AT SAMPLING AND TIME SINCE SAMPLED DEPLOYMENT/INJURY TO COMPLETING THE DPTGI. STANDARDISED COEFFICIENTS AND 95% CONFIDENCE INTERVALS SHOWN. CONFIDENCE INTERVALS THAT SUGGEST NON-SIGNIFICANT ASSOCIATIONS ARE DENOTED AS DOTTED LINES.

CHAPTER 4 TABLE 2: DIRECT AND INDIRECT EFFECTS OF COMBAT INJURY ON PTG THROUGH MEDIATING FACTORS OF PTSD, PTSD2, DEPRESSION AND PAIN.

Injury status	**Mediation status**	**Figure reference**	**Moderate degree of post-traumatic growth RRR (95%CI)**	**Large degree of post-traumatic growth RRR (95%CI)**
Overall injury group (versus uninjured group)	*Direct (unmediated)*	*Fig 2: c*	1.07 (0.80, 1.48)	1.59 (1.20, 2.19)
	Direct (mediated)	*Fig 2: c'*	1.09 (0.78, 1.53)	1.59 (1.17, 2.17)
	*Indirect: post-traumatic stress disorder symptoms**	*Fig 2: a1*b1*	1.14 (1.04, 1.31)	1.28 (1.12, 1.51)
	*Indirect: post-traumatic stress disorder symptoms^2**	*Fig 2: a2*b2*	0.94 (0.86, 1.01)	0.95 (0.86, 1.01)
	Indirect: Depression symptoms	*Fig 2: a3*b3*	0.93 (0.86, 0.98)	0.82 (0.70, 0.93)
	Indirect: Pain	*Fig 2: a4*b4*	1.06 (0.71, 1.58)	1.48 (1.04, 2.47)
Non-amputation injury (versus uninjured	*Direct (unmediated)*	*Fig 4: c*	0.99 (0.71, 1.40)	1.38 (0.97, 1.93)

Injury status	**Mediation status**	**Figure reference**	**Moderate degree of post-traumatic growth RRR (95%CI)**	**Large degree of post-traumatic growth RRR (95%CI)**
group)				
	Direct (mediated)	*Fig 4: c'*	1.01 (0.71, 1.46)	1.35 (0.92, 1.93)
	*Indirect: post-traumatic stress disorder symptoms**	*Fig 4: a1*b1*	1.24 (1.08, 1.50)	1.42 (1.19, 1.79)
	*Indirect: post-traumatic stress disorder symptoms^{2}**	*Fig 4: a2*b2*	0.89 (0.76, 0.98)	0.92 (0.80, 0.99)
	Indirect: Depression symptoms	*Fig 4: a3*b3*	0.90 (0.80, 0.97)	0.76 (0.60, 0.87)
	Indirect: Pain	*Fig 4: a4*b4*	1.02 (0.60, 1.62)	1.58 (0.98, 2.69)
Amputation injury (versus uninjured group)	*Direct (unmediated)*	*Fig 3: c*	1.39 (0.85, 2.55)	2.37 (1.37, 4.00)
	Direct (mediated)	*Fig 3: c'*	1.27 (0.75, 2.35)	2.18 (1.24, 3.75)
	*Indirect: post-traumatic stress disorder symptoms**	*Fig 3: a1*b1*	1.01 (0.92, 1.14)	1.02 (0.85, 1.25)
	*Indirect: post-traumatic stress disorder symptoms^{2}**	*Fig 3: a2*b2*	1.06 (0.99, 1.21)	1.06 (0.99, 1.22)
	Indirect: Depression symptoms	*Fig 3: a3*b3*	1.01 (0.94, 1.10)	1.03 (0.82, 1.28)

Injury status	**Mediation status**	**Figure reference**	**Moderate degree of post-traumatic growth RRR (95%CI)**	**Large degree of post-traumatic growth RRR (95%CI)**
	Indirect: Pain	*Fig 3: a4*b4*	1.21 (0.90, 2.15)	1.36 (0.98, 2.76)
Model adjusted for age at assessment, rank at sampling and time in years between sampled deployment/injury and completing the DPTGI. **To account for the curvilinear relationship between post-traumatic growth and post-traumatic stress disorder, post-traumatic stress disorders symptoms and post-traumatic stress disorder symptoms squared are included in the model.*				

Discussion

In this study we set out to report on PTG in a cohort of injured and uninjured UK Armed Forces personnel who deployed to Afghanistan and to understand the effect of sustaining a combat injury on subsequent PTG. After adjustment for confounders, the direct effect of sustaining a combat injury versus being uninjured was associated with a 59% increased relative risk of reporting a large degree of PTG compared to reporting no/a low degree PTG. The direct effect of sustaining an amputation injury versus being uninjured was associated with a 118% increased relative risk of reporting a large degree of PTG. In contrast, the direct effect of sustaining a non-amputation injury versus being uninjured was not associated with a large degree of PTG. While our models suggested that PTSD, depression and pain partially mediated the relationship between combat injury and a large degree of PTG, heterogeneity was noted between the indirect effects of different subtypes of injury (amputation and non-amputation injuries) on a large degree of PTG.

The ADVANCE study cohort has reported that those who sustained a non-amputation related injury reported significantly greater rates of depression, anxiety, PTSD and multimorbidity compared to an uninjured comparison group (13). Those with an amputation injury reported no significant differences in rates of poor mental health outcomes compared to the uninjured comparison group, and significantly less than their peers with non-amputation related injuries. In this analysis, we find those with an amputation injury were more likely to report a large degree of PTG and those with a non-amputation injury were no more likely to report a large degree of PTG compared to the uninjured group. A possible explanation for this disparity is that while both the amputation and non-amputation injury groups were both exposed to similar traumas (combat injury) and subsequent Defence Medical Service rehabilitation, the amputee group may have had increased access to other therapeutic or charitable services, which allowed them to facilitate more PTG (5). It is of particular note that the association between combat injury and reporting a large degree of PTG was only partially mediated by factors such as PTSD and depression. There is a suggestion therefore that PTG is more than just the absence of mental illness, though further work is needed to establish the validity and clinical meaningfulness of PTG (8, 25). Continued longitudinal investigation of this cohort might help elucidate whether these beneficial psychological outcomes are maintained over the long term, and whether they could be considered as a protective factor against poor mental health outcomes.

Much of the literature on PTG in military personnel who have sustained an amputation injury has focussed on US samples (16). Most suggest that amputees experience a moderate-large amount of PTG following their injury, though none of those research studies have referenced a suitable uninjured comparison group. The DPTGI has also been administered in a representative cohort study investigating the well-being of UK military personnel who deployed to Iraq/Afghanistan (6). In that cohort, the median score on the DPTGI was 13 (IQR 5, 24); factors such as sex, combat role, number of combat experiences, belief of being at serious risk of injury or death, reservist status, and better general health were associated with a moderate-large degree of PTG. In the ADVANCE study cohort, the median DPTGI score was far higher (28 (IQR 16, 39)). There are a number of possible explanations for this difference. Since belief of being at serious risk of injury/death has previously been shown to be associated with PTG (6, 14), it is unsurprising that the ADVANCE cohort would experience more PTG since approximately half of the cohort sustained a serious combat injury. Additionally, the ADVANCE cohort is primarily made up of combat personnel who likely experienced a greater number of combat experiences. Services such as the RAF and the Royal Navy are less represented in the ADVANCE cohort, and such services would have different deployment and combat experiences compared to the Army or Royal Marines. Interpretation of results from either cohort should be considered with this in mind.

There are clinical implications of our findings, which suggest that the experience of deployment related PTG may be more than just the absence of mental illness. The Medical Force Protection, the Armed Forces initiative to promote and maintain a healthy fighting force, might benefit from focussing not just on lowering risk of poor mental health outcomes, but also nurturing positive mental well-being. Further to this, understanding why amputees appear to report less poor mental health outcomes and increased positive mental health outcomes compared to injured non-amputees is an important future avenue of research. PTG is associated with better mental and physical health, as well as lifestyle factors such as increased use of physical exercise and lower use of alcohol or smoking (11), meaning that interventions that could elicit PTG might produce favourable psychological and physical health benefits (5). Increased efforts should be made to make these services accessible to those who require them, with our study suggesting that those who experienced non-amputation injuries during deployment being one such group who might benefit.

To the authors best knowledge, this study is the first to examine mental health and pain mediation pathways between combat injury and PTG. Pain was positively associated with a

large degree of PTG when investigating the whole cohort and mediation analysis showed that the relationship between combat injury and PTG was partially mediated by pain. One possible explanation for this is through rumination. Rumination on the trauma is a necessary component of PTG (16, 26) and has also been associated with increased pain intensity and pain catastrophising (27). It is possible that in our cohort, pain causes rumination on the participants' deployment experiences/injury, which could facilitate PTG. Whilst the general literature on PTG in those with a serious medical condition suggests that greater PTG is associated with lower pain (11), the evidence for this relationship varied depending on the nature of the study (e.g. cross-sectional versus longitudinal) or sample under investigation (e.g. type of serious medical issue). Given the known relationship between pain and other factors of general well-being and functioning (28), further investigation into pain and PTG amongst injured UK military personnel is warranted.

Strengths of the study include the use of a frequency matched uninjured group, matched to the injured group on important factors such as deployment era, age, rank and role in theatre (17). This allows for the study to explore deployment related PTG in a cohort with very similar experiences on deployment, with the exception of the injury itself. Additionally, this study employs a robust statistical approach including bootstrapping and GSEM to assess mediation, and addressing the curvilinear relationship between PTSD and PTG. Our study has several limitations. Just over a quarter of participants (27.0%) completed the PTG measure more than a year from their original ADVANCE study assessment. Whilst this is a limitation, longitudinal analysis has indicated that previous experience of PTSD is a significant predictor of PTG at future timepoints, indicating that the endorsement of post-traumatic distress at any point facilitates PTG (29). Another limitation is that whilst the response rate was reasonable, minor differences were noted between the responders and non-responders and the number of amputees was relatively small, requiring bootstrap analysis. Despite significant efforts to recruit from hard-to-reach populations, it is possible that groups such as those with worse current mental health or those with worse disability from injury would be less likely to volunteer or less able to take part in the ADVANCE study. The cross-sectional nature of this study only allows for investigation of association and not causation. Comparisons of the direct effect in the unmediated and mediated models were unlikely to produce interpretable increases/decreases in effect size also due to inconsistent mediation, and thus the total effect of the mediated model was not calculated. This study is limited to only the experience of PTG for male combat injured personnel, female experience of PTG

may well differ (6). Finally, our GSEM was unable to account for covariation between mental health and pain (30, 31).

Injured personnel in the ADVANCE cohort appear to be more likely to perceive beneficial psychological consequences from deployments to Iraq/Afghanistan, though it remains to be seen whether this is maintained in the long term when other health factors such as aging and poorer health-related functioning become more prevalent (32). Other events such as the Armed Forces withdrawal from Afghanistan and the Taliban's subsequent return to power might also affect the experience of PTG in this population. Those with amputation injuries appear to be more likely to report a large degree of PTG compared to a frequency matched uninjured group, whereas those with a non-amputation injury were no more likely to report a large degree of PTG. PTSD, depression and to a lesser extent pain each appear to play a mediating role in the relationship between combat injury and PTG.

Key messages

Evidence before this study:

- Positive psychological consequences of military deployment, such as Post Traumatic Growth (PTG), are relatively unexplored in the UK literature, especially in regard to physical combat injury.
- Physical combat injury is associated with greater rates of mental illness, but literature from the US has also found that military personnel who sustain a combat injury can also experience PTG.
- Reporting PTG is often associated with lower rates of reported pain and depression. PTG has a non-linear inverted U shape relationship with PTSD symptom severity.

Evidence from this study:

- 28.0% of the uninjured group and 36.9% of the injured group reported a large degree of PTG. 34.1% of the non-amputation injury subgroup and 45.4% of the amputation injury subgroup reported a large degree of PTG.
- UK Armed Forces personnel who sustained a combat injury while on deployment were more likely to report a large degree of PTG (relative to reporting no/a low degree of PTG) compared to the uninjured group.
- UK Armed Forces personnel who sustained an amputation injury were more likely to report a large degree of PTG (relative to reporting no/a low degree of PTG) compared to the uninjured group.
- UK Armed Forces personnel who sustained a non-amputation injury were no more likely to report a large degree of PTG (relative to reporting no/a low degree of PTG) compared to the uninjured comparison group.
- Depression and Posttraumatic CheckList (PCL) scores[2] (which represent greater Post-Traumatic Stress Disorder (PTSD) symptom severity in the statistical models) were associated with a lower likelihood of reporting a large degree of PTG. Current moderate-extreme pain and PCL scores (which represent lower PTSD symptom severity in the statistical models) were associated with a greater likelihood of reporting a large degree of PTG.
- Depression, PTSD and current moderate-extreme pain partially mediated the relationship between combat injury and reporting a large degree of PTG.
    - PTSD and depression partially mediated the relationship between sustaining a non-amputation injury and reporting a large degree of PTG.

- Sustaining an amputation injury was not associated with depression, PTSD or current moderate-extreme pain and as such no mediation occurred for this group.

Strengths of this study:

- Strengths of the study include the use of a frequency matched uninjured group and strong analytical approach including both generalised structural equation modelling incorporating multinomial logistic regression and bootstrapping.

Limitations of the study:

- Just over a quarter of participants completed their PTG measure over a year from their ADVANCE assessment.
- Whilst the response rate was reasonable, the total number of those who completed the study with an amputation injury was relatively small.
- Minor differences in characteristics of those who responded vs those who did not respond to the IMPACTS study are noted.
- Those with the worse physical or psychological health may have had difficulty in attending a full study day at the Defence Medical Rehabilitation Centre and so there may be a response bias.
- Covariance between pain and depression/PTSD could not be accounted for due to limitations of the generalised-structural equation modelling approach.

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The underlying mechanisms by which PTSD symptoms are associated with cardiovascular health in male UK military personnel
"A diverse number of symptoms, not just hyperarousal, are suggested as the most relevant symptom clusters associated with cardiometabolic effects and haemodynamic functioning."

Overview

In this chapter, I will address aims 3.1 and 3.2 by describing the observed association between PTSD symptom clusters and cardiovascular risk factors in the ADVANCE study cohort. The chapter first introduces the topic of PTSD and the potential mechanisms by which it can affect cardiovascular health. The methodology of variable selection procedures and robust regression modelling is then explained and applied. Results of the study are followed by discussion of the findings that a diverse number of symptoms best explain associations between PTSD and cardiovascular health, the confounding effect of dissociative symptoms and lifestyle factors, and potential clinical implications of the study.

Aim 3.1 Examine whether PTSD symptom clusters are associated with cardiovascular risk factors including inflammation, cardiometabolic effects and haemodynamic functioning in a cohort of injured/uninjured Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).

Aim 3.2 Assess the relative importance of these symptom clusters via variable selection procedures and confirm results via robust regression modelling.

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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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Competing interests

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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.

Keywords: Military Personnel; Heart Disease Risk Factors; Stress Disorders, Post-Traumatic; Inflammation; Hemodynamics; ADVANCE cohort

Acronyms: 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

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 (1, 2). PTSD is characterised by symptoms such as intrusive thoughts, avoidance behaviours, emotional numbing and hyperarousal (3). 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 (4, 5). 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 (6). It is through these alterations that PTSD has also been linked to poor physical health outcomes, including Cardiovascular Disease (CVD) (7).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) (5). 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 (8). Hyperarousal symptoms are theorised to be primarily responsible for alterations in the nervous system (6, 9), though few studies have investigated links between symptom clusters and CVD risk (10). Proposed biological mechanisms include increased inflammation, cardiometabolic effects, and changes to haemodynamic functioning (11-13).

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 (12). 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 (5, 14).

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 (15, 16). 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 (13). There is however, uncertainty in the direction and magnitude of the association between PTSD and SBP (17).

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 (11). 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 (18).

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. Depending on the included variables, interpretation of the effects of independent variables on dependent variables can change distinctly, 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 (19-21). A second step including model averaging is suggested as a method of addressing model uncertainty (19). 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) (19, 20).

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 (22). Along with measures of mental well-being, the ADVANCE study cohort completed a comprehensive health suite of assessments including cardiovascular health (23).

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.

Methods

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 (24). 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) (24). 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.

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 hours prior to venous blood sampling and Vicorder assessment).

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.

Materials

Exposure

POST-TRAUMATIC STRESS DISORDER

PTSD was measured using the PTSD Clinical Checklist (PCL-C), a 17-item measure of PTSD (25). Scores range from 17-83. Probable PTSD was defined as a score ≥50, a cut off with good diagnostic accuracy in military populations (26). The four factor solution based on the DSM-IV criteria was used (3): 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).

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 0.10mg/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 five minutes 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 (27), if PWV readings differed from one another by 0.5m/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 (28). 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 (29). Estimated Glucose Disposal Rate (eGDR) was used as an indicator of insulin resistance as previously described (23). 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 (≥140mmHg) and DBP (≥90mmHg). 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 (30).

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.

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) (23).

MEDICATION

Participants' self-reported current medication use during the clinical interview. Medications were coded using the Anatomical Therapeutic Chemical Classification Index 2020 (31). 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) (32).

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 (23, 33-35). In line with best

practice, spearman's correlations were calculated between all variables of interest (19, 20). Moderate correlations were defined as correlations ≥0.4 and <0.7, and strong correlations were defined as ≥0.7. Classification of normal clinical ranges for each outcome can be found in Chapter 5 Supplementary Materials 1. Symptom clusters were assessed as part of this analysis regardless of probable PTSD status (PCL score ≥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 (36). 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 (19, 20) (Figure 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 ≥30% were assessed for co-dependence via χ^2 of the 2x2 inclusion

frequency tables, then, if assessed as independent, went on to the second step (21). No co-dependency issues were noted and so no strategy was implemented to address co-dependence (Chapter 5 Supplementary Materials 2). 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 ($p<0.05$).

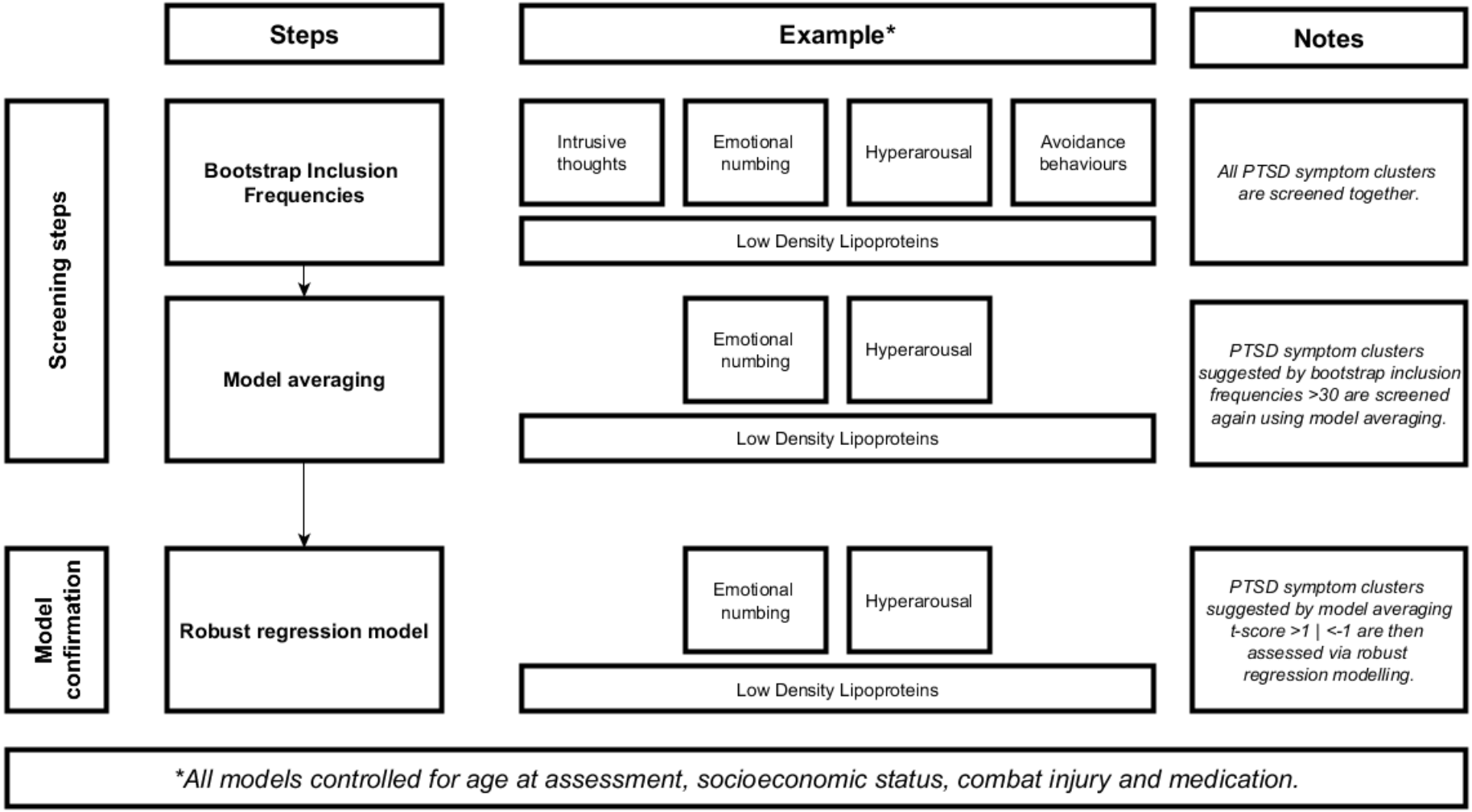
Robust regression modelling

Associations suggested by the variable selection procedures were confirmed via the use of robust regression using MM maximum likelihood type estimation (37). 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 (38). 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.

CHAPTER 5 FIGURE 1:VARIABLE SELECTION PROCEDURES



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%).

Chapter 5 Supplementary Materials 3 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 Chapter 5 Supplementary Materials 2. 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 Chapter 5 Supplementary Materials 4.

Chapter 5 Table 2 reports the associated robust regression coefficients between each symptom cluster and cardiovascular risk factor selected by the 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. Chapter 2 Figures 2-6 visualises the linear and non-linear relationships between the symptom clusters and their associated cardiovascular risk outcomes. Chapter 5 Supplementary Materials 5 shows the figures for variables not confirmed by robust regression modelling.

CHAPTER 5 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	**9.00 (6.00, 13.00)**	**8.00 (6.00, 11.00)**	**20.00 (18.00,**

	Overall sample (*n*=1111)	**No PTSD (*n*=973)**	**Probable PTSD (*n*=138)**
Median (IQR)			**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 normal ranges*			
Inflammation			
HsCRP (mmol/l) Median (IQR) *Normal range <1.0mmol/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: <80mmHg*	**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: <120mmHg*	**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: 4.2-9.4m/s*	**7.77 (7.07, 8.70)**	**7.77 (7.03, 8.70)**	**7.77 (7.07, 8.80)**
Cardiometabolic effects			

	Overall sample (*n*=1111)	**No PTSD (*n*=973)**	**Probable PTSD (*n*=138)**
Triglycerides (mg/dl) Median (IQR) ***Normal triglycerides: <150mg/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: <200mg/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: 40-60mg/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-Density Lipoproteins: <130mg/dl***	**116.01 (96.68, 139.21)**	**116.01 (96.68, 139.21)**	**112.14 (96.68, 139.21)**
HbA1c (mmol/mol) Median (IQR) ***Normal: <42mmol/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 ≤8.77mg/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: <100cm^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			

CHAPTER 5 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* coefficient (95% bias-corrected confidence interval)	Model 2** coefficient (95% bias-corrected confidence interval)
Pulse Wave Velocity	**Avoidance behaviours (score range from 2-10)**	**0.038 (0.000, 0.080)**	**0.033 (-0.008, 0.076)**
Systolic blood pressure	**Avoidance behaviours (score range from 2-10)**	**0.785 (0.189, 1.309)**	**0.640 (0.065, 1.149)**
Insulin resistance	**Emotional numbing (score range from 5-25)**	**-0.031 (-0.047, -0.162)**	**-0.021 (-0.036, -0.005)**
Low-Density Lipoproteins	**Emotional numbing (score range from 5-25)**	**0.389 (-0.368, 1.098)**	**0.476 (-0.237, 1.358)**
	Hyperarousal (score range from 5-25)	**-0.612 (-1.272, 0.068)**	**-0.553 (-1.222, 0.122)**
High-Density Lipoproteins	**Hyperarousal (score range from 5-25)**	**-0.247 (-0.371, -0.119)**	**-0.122 (-0.267, 0.016)**
(Log)Triglycerides* **	**Hyperarousal (score range from 5-25)**	**1.015 (1.008, 1.021)**	**1.009 (1.002, 1.017)**
High-Density Lipoproteins	**Intrusive thoughts (score range from 5-25)**	**-0.299 (-0.454, -0.154)**	**-0.159 (-0.312, 0.002)**

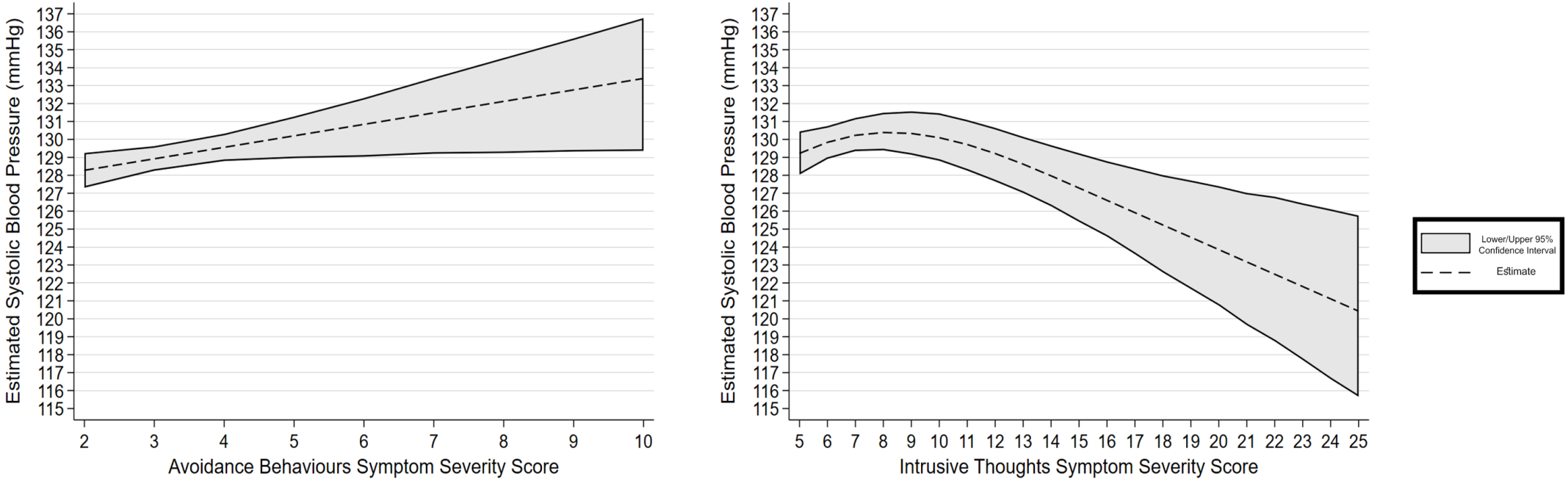
Cardiovascular risk outcome	**Post-Traumatic Stress Disorder symptom cluster**	**Model 1* coefficient (95% bias-corrected confidence interval)**	**Model 2** coefficient (95% bias-corrected confidence interval)**
Visceral Adipose Tissue	**Intrusive thoughts (score range from 5-25)**	**0.862 (0.312, 1.539)**	**0.574 (0.020, 1.250)**

***Univariable model including PTSD symptom cluster.**

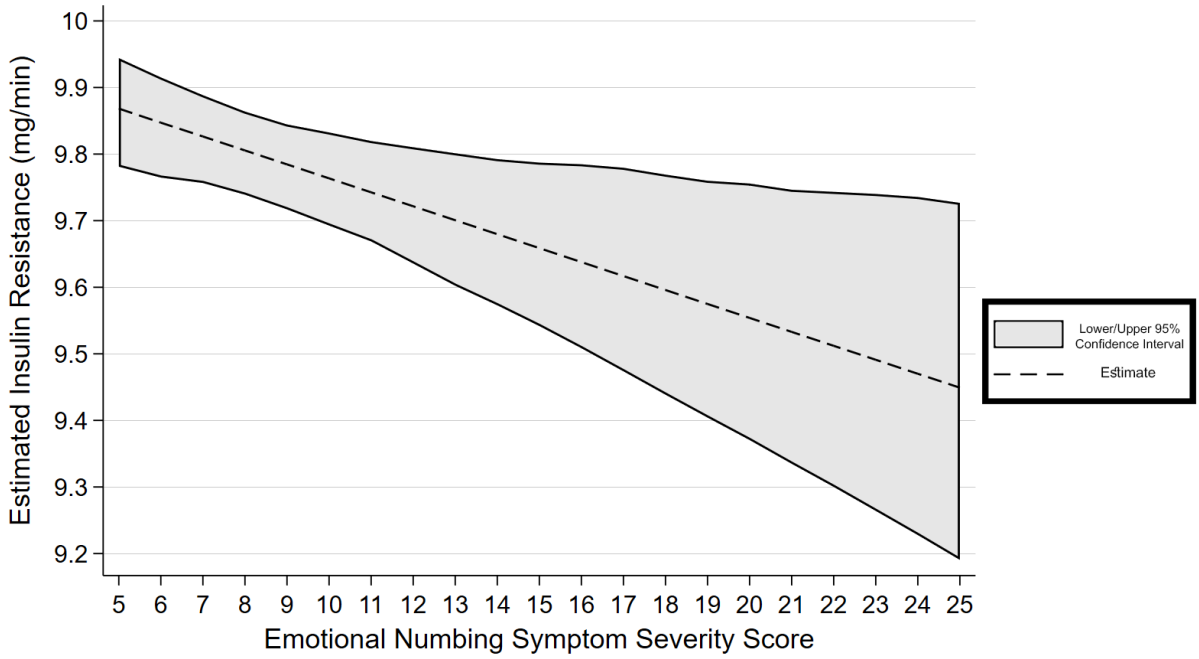
****Multivariable model including PTSD symptom cluster and confounders (age at assessment, combat injury, medication use and socioeconomic status).**

*****Coefficients are exponentiated and refer to percentage change in geometric mean of triglyceride levels. E.g. 1.015=1.5% increase.**

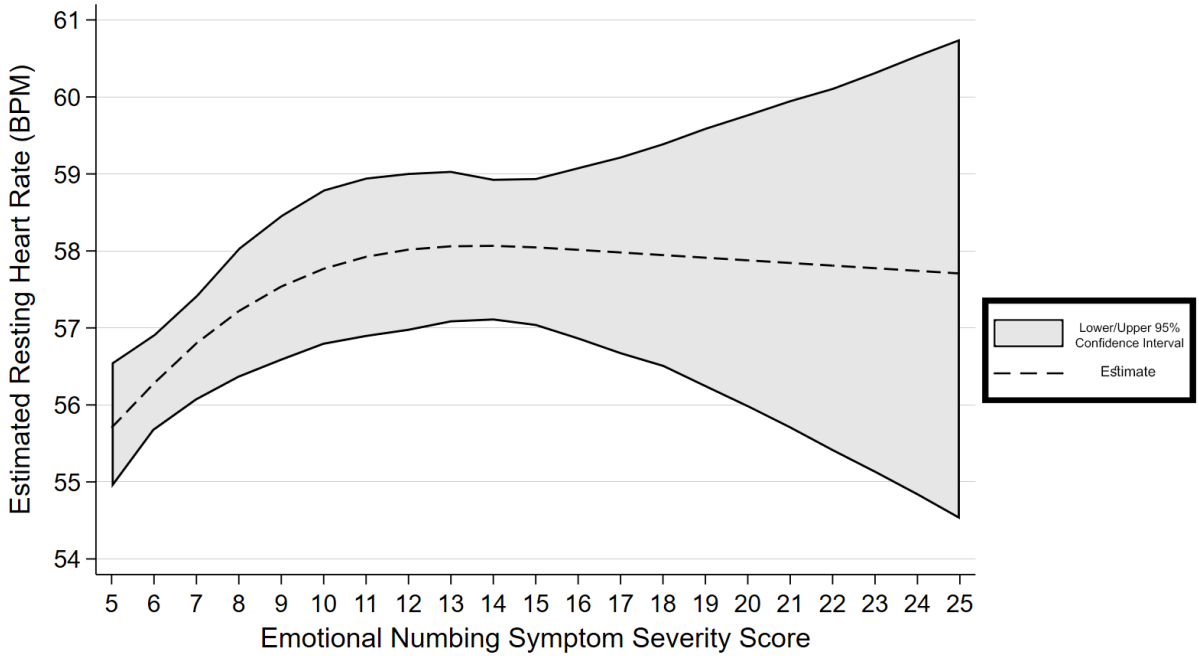
CHAPTER 5 FIGURE 2: ESTIMATED MARGINAL EFFECTS OF POST-TRAUMATIC STRESS DISORDER SYMPTOM CLUSTERS SELECTED FOR THE SYSTOLIC BLOOD PRESSURE MODEL BY VARIABLE SELECTION PROCEDURES AND CONFIRMED BY ROBUST REGRESSION MODELLING



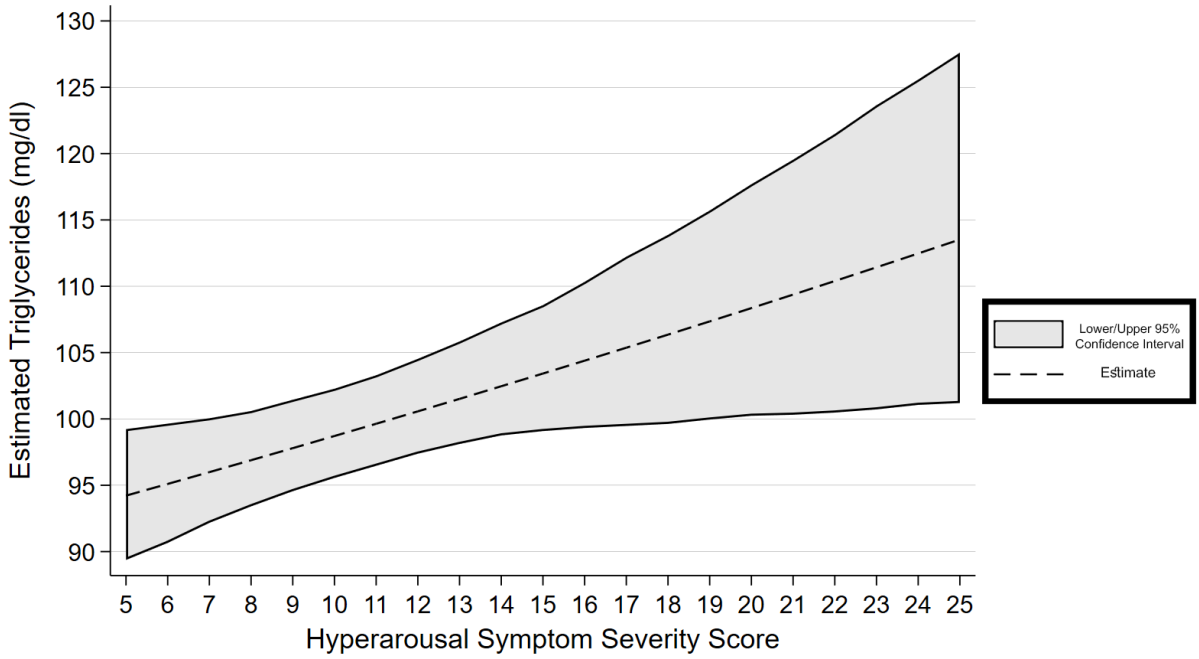
CHAPTER 5 FIGURE 3: ESTIMATED MARGINAL EFFECTS OF POST-TRAUMATIC STRESS DISORDER SYMPTOM CLUSTERS SELECTED FOR THE INSULIN RESISTANCE MODEL BY VARIABLE SELECTION PROCEDURES AND CONFIRMED BY ROBUST REGRESSION MODELLING



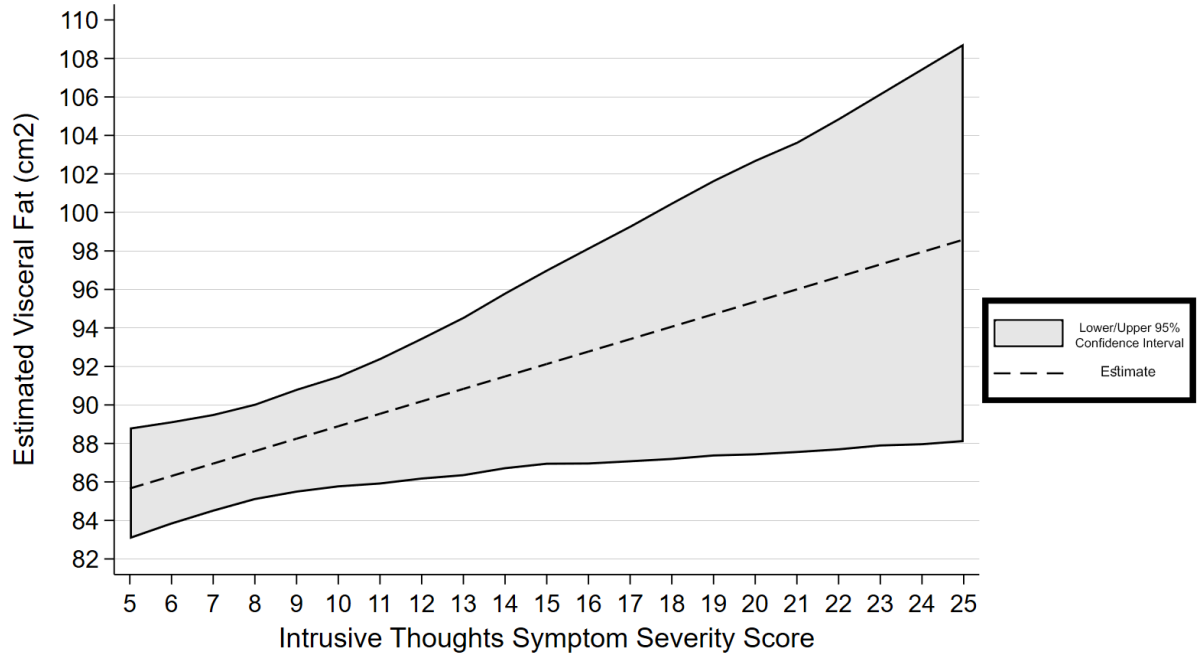
CHAPTER 5 FIGURE 4: ESTIMATED MARGINAL EFFECTS OF POST-TRAUMATIC STRESS DISORDER SYMPTOM CLUSTERS SELECTED FOR THE RESTING HEART RATE MODEL BY VARIABLE SELECTION PROCEDURES AND CONFIRMED BY ROBUST REGRESSION MODELLING



CHAPTER 5 FIGURE 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



CHAPTER 5 FIGURE 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



Discussion

In this study we aimed to assess the association between PTSD symptom clusters and cardiovascular risk and hypothesised 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 were limited as whilst it was selected by variable selection procedures, it was 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 (39-41). Unique neurobiological features of the dissociative subtype of PTSD are theorised to be responsible for the blunted autonomic response (42). 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 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 (43). Emotional numbing is theorised to be a product of over stimulation of these hyperarousal symptoms, which result in emotional exhaustion/depletion of cognitive resources (44). 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 (45). 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 (46). 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 (47, 48). 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 (49). 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 (23). 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' (50). 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 (51). 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 (39-41). 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 (48). 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 (22). 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 (52).

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.

Key messages

Evidence before this study:

- Post-Traumatic Stress Disorder (PTSD) has been observed to be associated with greater rates of cardiovascular disease and worse cardiovascular risk profiles. These associations appear to exist independently of depressive symptoms.
- The hypothesised reason for this is through the experience of hyperarousal symptoms, though few studies have investigated the association between different symptom clusters and cardiovascular risk factors.

Evidence from this study:

- A diverse number of PTSD symptoms were found to be associated with worse cardiovascular risk profiles, not just hyperarousal.
- Greater scores on the avoidance behaviours subscale were associated with higher systolic blood pressure. Greater scores on the intrusive thoughts subscale were associated with higher insulin resistance and had a non-linear relationship with systolic blood pressure. Greater scores on the hyperarousal subscale were associated with higher triglyceride levels. Greater scores on the emotional numbing subscale had a non-linear relationship with heart rate.

Strengths of the study:

- Strengths include the investigation of a range of cardiovascular risk factors in a relatively young cohort and the use of a rigorous statistical approach for variable selection procedures alongside bootstrapping.

Limitations of the study:

- Use of the PCL-C which is based on the DSM-IV, not the current DSM-V classification of PTSD.
- The DSM-V acknowledges different subtypes of PTSD, including a dissociative subtype. Those who experience dissociative symptoms have been observed to have different cardiovascular risk profiles to those with the hyperarousal subtype of PTSD. This might explain the non-linear relationships noted, particularly with emotional numbing and heart rate, however no measures of dissociative symptoms were used in this analysis.
- PTSD is a heterogenous disorder. Mediating/moderating factors, such as lifestyle effects (e.g. diet, physical exercise) or comorbid depressive symptoms were not accounted for.

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6
The underlying mechanisms by which Post-Traumatic Growth is associated with cardiovascular health in male UK military personnel
"Positive psychological outcomes have beneficial properties even amongst the relatively healthy, however it is also true that post-traumatic growth was associated with both better and worse cardiovascular risk profiles".

Overview

In this chapter, I will address aims 4.1 and 4.2 by describing the observed associations between factors of PTG and cardiovascular risk factors in the ADVANCE study cohort. The chapter first introduces the topic of positive psychology/psychological thriving and the mechanisms by which it can affect cardiovascular health. The methodology of variable selection procedures and robust regression modelling are explained and applied. Results of the study are followed by discussion of the findings that factors of PTG are associated with mostly positive but also some negative indicators of cardiovascular health and the known associations between spirituality and cardiovascular health.

Aim 4.1 Examine whether factors of PTG will be associated with better cardiovascular health indicators including inflammation, cardiometabolic effects and haemodynamic functioning in a cohort of injured/uninjured Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).
Aim 4.2 Assess the relative importance of the factors of PTG in these associations via variable selection procedures and confirm results via robust regression modelling.

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The underlying mechanisms by which Post-Traumatic Growth is associated with cardiovascular health in male UK military personnel: The ADVANCE cohort study

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Abstract

Post-Traumatic Growth (PTG) is associated with better physical health, but the mechanisms of this are poorly understood. This cross-sectional analysis uses novel variable selection methodology (bootstrap inclusion frequencies and model averaging) and robust regression modelling to assess whether factors of PTG (Appreciation of Life, New Possibilities, Personal Strength, Relating to Others and Spiritual Change) are associated with cardiovascular health including cardiometabolic effects, haemodynamic functioning and inflammation in a cohort of male UK military personnel. Analysis was performed on 1006 participants (median age 34). The findings suggest that factors of PTG are associated with mostly positive cardiometabolic effects and haemodynamic functioning but also with some negative indicators of cardiovascular health. No factors were associated with inflammation. This paper highlights how positive psychological functioning is associated with objective measures of physiological health, and we discuss the potential direction of future research to understand why both positive and negative associations were observed.

Introduction

The understanding of disorders such as depression, anxiety, Post-Traumatic Stress Disorder (PTSD) and other negative responses to stress or trauma, along with interventions and treatments for these pathologies, has progressed significantly over the past century. However, a focus on mental illness limits our understanding of the full spectrum of mental health, both positive and negative, and its associations with physical health (1). Investigation into aspects of positive psychology has increased in recent years, with more attention being paid to the full range of human experience, inclusive of psychological thriving rather than just pathology.

Post-Traumatic Growth (PTG) is one such aspect of psychological thriving which has received notable attention in the scientific community. PTG refers to beneficial psychological change following trauma. One of the most used measure of PTG, the PTG-Inventory, determines PTG through five factors: a greater Appreciation Of Life (AOL), seeing New Possibilities (NP) in one's future, an increase in one's perception of their own Personal Strength (PS), Relating To Others (RTO) better and positive Spiritual Change (SC) (2, 3). PTG has been shown to be prevalent amongst many trauma survivors, including those exposed to warzones and life-threatening illnesses (4, 5). Importantly, PTG has been shown that it can be elicited through psychological intervention, meaning those that experience negative reactions to traumatic events, such as PTSD, can be helped to build beneficial psychological changes alongside treating and minimising the symptoms of PTSD (6).

The pathology of mental illness has been linked to physical illness. For example, PTSD has been shown to be associated with Cardiovascular Disease (CVD) through risk factors such as inflammation, cardiometabolic effects and haemodynamic functioning (7). Positive psychology is theorised to affect these physiological dimensions through increases in restorative processes such as sleep, physical activity and diet, or functioning as a protective

factor against deleterious functions such as stress/cortisol response (8-10). Positive psychological constructs, including optimism (a perspective that life ahead will be good), positive affect (the extent of which a person feels positive emotions), resilience (going through a trauma and having no negative psychological consequences as a result) and PTG, have been found to be associated with better cardiovascular health (11-14). In those with established CVD, positive psychological interventions including optimism training have been found to lower cortisol and inflammatory response (14-16). In those without established CVD, PTG and positive psychological functioning have been found to be associated with positive lifestyle factors such as better physical fitness or smoking (11), and better cardiovascular risk profiles including better haemodynamic functioning (17, 18), cardiometabolic effects (19, 20) and inflammation (21). There remains a question as to whether measuring these positive psychological constructs and their association with physical health are actually just measuring the absence of negative constructs (e.g. depression, anxiety or PTSD) (14). To the authors best knowledge, no studies have investigated the psychological mechanisms by which PTG might affect cardiovascular risk indicators through investigation of the five factors of PTG.

The ADVANCE cohort is a large study of UK military personnel, approximately half of which sustained a physical combat injury and half are a frequency-matched uninjured comparison group (22). Using variable selection procedures including Bootstrap Inclusion Frequencies (BIF) and model averaging, novel statistical approaches to reduce bias in models through the inclusion/exclusion of pertinent variables (23, 24), a recent investigation using the ADVANCE cohort data found that PTSD symptom clusters were associated with cardiovascular risk factors including cardiometabolic effects and haemodynamic functioning (25), but not inflammation (specifically inflammatory marker High-sensitivity C-Reactive

Protein (HsCRP). PTG has also been investigated in this cohort, with 28% of the uninjured group and 36% of the injured group experiencing a large degree of PTG (26).

Based on the emerging scientific literature that suggests positive psychology is associated with better cardiovascular health, we hypothesise that PTG will be associated with better cardiovascular health indicators including inflammation, cardiometabolic effects and haemodynamic functioning. We aim to assess the relative importance of the factors of PTG in these associations via variable selection procedures and confirm results via robust regression modelling.

Methods

Participants

This study is secondary data analysis from the baseline data collection of the ADVANCE cohort study, a longitudinal investigation into the long-term health impact of sustaining a battlefield injury (22). Participants consisted of 579 physically injured and 566 uninjured UK military personnel who deployed to Afghanistan. The uninjured group were frequency-matched to the injured group based on sex, age, rank, role on deployment, regiment and deployment era.

Procedure

Participants were assessed at the UK Defence Medication Rehabilitation Centre (DMRC) Headley Court (2015-2018) or Stanford Hall (2018-2020). The ADVANCE assessment day included a comprehensive health assessment including self-report questionnaires, a research nurse-led clinical interview, Vicorder assessment, bloodwork, and Dual-Energy X-ray Absorptiometry (DEXA). A measure of PTG was introduced to the study in 2018. From this point, participants completed the questionnaire as part of their ADVANCE assessment. Participants who attended prior to this date were invited to complete the questionnaire either online or via post.

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.

Materials

Post-Traumatic Growth

PTG was assessed using the Deployment-related Post-Traumatic Growth Inventory (DPTGI), a military deployment variant of the Post-Traumatic Growth Inventory (2, 26, 27). The stem question relates to "as a result of my deployments to Iraq or Afghanistan since 2002:". The measure contains 21 items and scores range from 0-63. The five-factor scoring method includes: AOL (*n*=3 items; score 0-9), NP (*n*=5; score 0-15), PS (*n*=4 items; score 0-12); RTO (*n*=7 score 0-21) and SC (n=*2* items; score 0-6). Cronbach's alpha for the measure was 0.94, with the factors ranging from 0.73 (SC) to 0.88 (RTO).

Anxiety

Anxiety was assessed using the Generalised Anxiety Disorder-7 (GAD), which contains seven items and scores ranging from 0-21 (28). Probable anxiety was defined as a score of ≥10.

Depression

Depression was assessed using the Patient Health Questionnaire-9 (PHQ), which contains nine items and scores ranging from 0-27 (29). Probable depression was defined as a score of ≥10.

Post-Traumatic Stress Disorder

PTSD was assessed using the PTSD Clinical Checklist (PCL-C). The measure has 17 items and scores range from 17-83 (30). Probable PTSD was defined as a score of ≥50.

Outcomes

Classification of normal clinical ranges for each cardiovascular outcome can be found in supplementary materials 1.

Inflammation

High-sensitivity C-Reactive Protein (HsCRP)

Venous blood sampling was conducted on-site and assayed at a local NHS laboratory. HsCRP was measured in mg/l, with a lower detection limit of 0.10mg/l.

Haemodynamic functioning

Vicorder assessment

Participants were laid in a supine positive at a 30-degree angle for a Vicorder (Skidmore Medical, UK) assessment. After a five-minute rest period, participants had assessments of diastolic and systolic blood pressure along with resting heart rate, and pulse wave velocity. Measurements were taken three times by a research nurse in a temperature-controlled environment. Resting heart rate (Beats Per Minute (BPM)) and brachial systolic/diastolic blood pressure (millimetres of mercury (mmHg)) were taken during pulse wave analysis, assessed from the cuff of the left upper arm and left thigh. Pulse wave velocity (metres per second (m/s)) was assessed from the cuff of the left upper arm and neck. Mean values across the three readings were taken as per recommended guidance (31), however if pulse wave velocity readings differed by ≥0.5m/s, the median value was taken. Similarly, for blood pressure and heart rate readings, the median was taken if readings differed by 2.5x the median absolute deviation (32). Observations where all three readings were greater than 2.5x the median absolute deviation were removed from the analysis (the number of excluded observations ranged from 15 (resting heart rate) to 53 (pulse wave velocity)).

Cardiometabolic effects

Venous blood sampling was undertaken in the morning of the participant's appointment. Participants fasted for at least eight hours prior to venous blood sampling, including no caffeine or alcohol. Blood plasma and serum samples were assayed at local NHS laboratories.

Blood glucose and insulin resistance

Fasting glycated haemoglobin ($HbA1_C$) was measured in mmol/mol. Conversion to $HbA1_C$ % was conducted for the purposes of estimating insulin resistance using the International Federation of Clinical Chemistry-National Glycohemoglobin Standardisation Program equation (33). Estimated Glucose Disposal Rate (eGDR) was used as an indicator of insulin resistance (34). Lower eGDR is reflective of greater insulin resistance and is measured in milligrams/kilograms per minute (mg/kg/min). eGDR 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 medication use with the indication of hypertension, or current high blood pressure defined as systolic blood pressure (≥140mmHg) and diastolic blood pressure (≥90mmHg).

Dyslipidaemia

Triglycerides, total cholesterol, High-Density Lipoproteins (HDL), Low-Density Lipoproteins (LDL) were assessed from blood samples in mmol/l. HDL refers to lipids that absorb other cholesterol for processing/recycling in the liver, and higher levels of HDL is associated with lower CVD risk (35). LDL cholesterol refers to cholesterol that circulates in the body for depositing inside or artery walls/cell-repair. Higher levels of LDL are associated with greater CVD risk (35). Data was transformed to mg/dl for the purposes of this study to increase interpretability (36).

Obesity

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

Confounders

Age

Age was measured at time of the ADVANCE assessment in years.

Combat injury

Combat injury details were collected from electronic medical records provided by the Ministry of Defence Defences Statistics (Health) department and supplemented by self-report data collected during the clinical interview section. Combat injury was categorised as uninjured or injured (37).

Medication

Self-reported current medication use was collected during the clinical interview. The Anatomical Therapeutic Chemical Classification Index (38) was used to code medications. Medications of interest for this current study included medications with a primarily cardiovascular or mental health effect including: anti-gout preparations; 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; psychoanaleptics (drugs that produce a calming mental health effect) and psycholeptics (drugs that provide a stimulating mental health effect). Medication use was categorised as ‘not on medication of interest’ and ‘on medication of interest’.

Socioeconomic status

Socioeconomic status was categorised based on rank at time of sampling; junior non-commissioned officer rank (NATO OR2-OR4), senior non-commissioned officer rank (NATO OR5-OR9) and commissioned officer rank (NATO OF1-OF6) (39).

Data analysis

Data analysis was conducted using STATA 17.0. Confounders, based a-priori on the literature, included age, combat injury, medication of interest and socioeconomic status (34, 40-42). Regression diagnostics were completed on linear regression models including all centred PTG factors and each outcome to assess normality of residuals, influential observations (Cook's D) and multicollinearity (variance inflation factor). Variables were transformed if residual normality was not achieved. HsCRP and triglycerides achieved residual normality after log-transformation. Coefficients for log-transformed outcomes were exponentiated and reflect a percentage change in geometric mean of the outcome for each unit increase of the PTG factor score. Residual outliers were defined as Cook's $D>4/n$, where n is the sample size. Presence of residual outliers ranged from 3.79% for $HbA1_C$ (n=37) to 11.0% for pulse wave velocity (n=105). During the diagnostic stage, non-linear relationships were investigated via inspection of the augmented component plus residual plot. Factors with plots suggestive of non-linear associations were transformed into a restricted cubic spline with three knots. A univariable linear regression model and subsequent likelihood ratio test ($p<0.05$) was conducted between the PTG factor and the restricted cubic spline function of the factor with the cardiovascular risk outcome to confirm which function better fit the data. Spearman's correlation coefficients were generated between all variables of interest. Moderate associations were defined as spearman's correlation coefficients between 0.4 and 0.7 and strong associations were defined as >0.7.

To address the aims of the study, variable selection procedures were conducted in line with recommendations from the literature (23, 24). First a screening step was conducted using BIF to assess model stability including all PTG factors and confounders. 1000 replications were used. To understand whether factors of PTG might be competing for selection through co-dependence, factors with BIF≥30% were assessed for independence based on a chi^2 analysis of BIF. Factors which were found to have been included due to co-dependence were removed based on suggested practice for removal of co-dependent variables with weak associations (43). Variables selected after screening were then subjected to Weighted Absolute Least Square (WALS) model averaging, bootstrapped with 1000 replications. Finally, to assess whether a model with individual or multiple PTG factors best fit the data, a likelihood ratio test was conducted (p<0.05). Variable selection procedures were repeated excluding residual outliers.

Robust regression models using MM maximum likelihood type estimation (44) were generated to confirm associations suggest by the variable selection procedure. PTG factors with identified non-linear associations were entered into models as restricted cubic spline functions. Models were estimated at a univariable level, at a multivariable level including confounders and at a multivariable level including confounders and excluding participants with probable anxiety, depression or PTSD. The third model is included due to potential confounding from the known curvilinear relationship between PTSD and PTG (45), and to assess whether the associations with PTG were apparent in the absence of mental ill health. All models were bootstrapped with at least 1000 replications and bias-corrected confidence intervals are reported.

Missing values ranged from three (PHQ; <1%) to 73 (insulin resistance; 6.3%). One item of the DPTGI was missing for 400 participants due to an administration error. One item was missing for 430 participants, two items were missing for three participants and three items

were missing for one participant. Value were imputed using two way imputation for participants with ≤3 items missing from the DPTGI (46). All other dependent variable missing data was handled using casewise deletion (range min: visceral adipose tissue *n*=9 (<1.0%) max: LDL *n*=50 (<5.0%)). Exclusion criteria for the current study included experiencing significant injury not related to his military service (*n*=1), not completing the DPTGI (*n*=108), >3 items missing on DPTGI (*n*=2), or elevated HsCRP levels suggestive of current infection (*n*=30).

Results

1006/1145 participants of the ADVANCE cohort were included as part of this analysis. A breakdown of the characteristics of participants who completed/did not complete the DPTGI can be found in supplementary materials 2. 73.0% of participants (*n*=756) completed the DPTGI on the day of their appointment or <12 months after their appointment, and 27.0% (*n*=277) completed the DPTGI>12 months after their appointment. Chapter 6 Table 1 shows the demographic characteristics of this sample. The median age of the sample was 34, with the majority of the sample being junior non-commissioned officers (*n*=650; 64.6%), had not sustained a combat injury (*n*=505; 50.2%), and were not on a cardiovascular or mental health medication of interest (*n*=901; 90.6%). Sertraline was the most common mental health medication of interest (*n*=24) and allopurinol was the most common cardiovascular medication of interest (*n*=5). 24.5% (*n*=246) reported either probable depression, anxiety or PTSD. Spearman's correlation coefficients between all PTG factors, confounders and cardiovascular risk outcomes can be found in supplementary materials 3. Moderate-strong correlations were noted between all PTG factors with the exception of SC, which had low-moderate correlation with other PTG factors.

Variable selection procedures can be found in supplementary materials 4. No associations were observed between any factor of PTG and HsCRP, pulse wave velocity or resting heart

rate. AOL was selected for outcomes of diastolic blood pressure, HDL and triglycerides. NP was selected for outcomes of systolic blood pressure, $HbA1_C$ and visceral adipose tissue. PS was selected for outcomes of LDL and total cholesterol. RTO was selected for outcomes of total cholesterol and insulin resistance. SC was selected for outcomes of diastolic blood pressure, total cholesterol, $HbA1_C$, LDL and insulin resistance. A non-linear relationship was identified between NP and systolic blood pressure. Co-dependency was noted between PS and SC with both total cholesterol and LDL. PS was retained for LDL and SC was retained for total cholesterol.

Chapter **6 TABLE 2** reports the associated robust regression coefficients and 95% bias-corrected confidence intervals between each PTG factor and cardiovascular risk factors selected by variable selection procedures. After accounting for confounders, greater scores on the factor of AOL were confirmed as having an association with lower diastolic blood pressure, greater HDL and lower triglyceride levels. Greater scores on the factor of NP were confirmed to be associated with lower HDL and had a non-linear relationship with systolic blood pressure. Greater scores on the factor of PS were confirmed to have an association with lower LDL. Greater scores on the factor of RTO were confirmed to have an association with lower total cholesterol. Greater scores on the SC subscale were confirmed to have an association with higher $HbA1_C$. Chapter 6 Figures 1-5 presents the marginal effect associations between PTG factors and cardiovascular health indicators confirmed to have an association via robust regression modelling. Limited evidence for associations were present for some factors due to being selected by variable selection procedures but not confirmed by robust regression modelling. Supplementary materials 5 shows the marginal effects that were not confirmed during robust regression modelling.

In the model excluding those with mental illness (e.g. probable depression, anxiety or PTSD), increases in the size of coefficients were noted for associations between greater scores on the

AOL subscale with lower diastolic blood pressure, greater scores on the AOL subscale with greater HDL and greater scores on the NP subscale with lower HDL (Chapter 6 Table 2). No or minor changes were noted in the coefficients for SC with $HbA1_C$, RTO with total cholesterol and AOL with triglycerides. Whilst the coefficient increased for PS with LDL in this model, so did the width of the confidence intervals, which now include zero.

CHAPTER 6 TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF SAMPLE

	Overall sample
Total sample *No. (%)*	1006 (100.00%)
Demographics	
Age in years at assessment Median (IQR)	34 (30, 37)
Ethnicity	
White *No. (%)*	912 (90.66)
All other ethnic minorities *No. (%)*	94 (9.34)
Rank	
Junior Non-Commissioned Officer rank *No. (%)*	650 (64.61)
Senior Non-Commissioned Officer rank *No. (%)*	228 (22.66)
Commissioned Officer rank *No. (%)*	128 (12.72)
Combat injury	
Yes *No. (%)*	501 (49.80)
On Medication of interest	
Yes *No. (%)*	95 (9.44)
Cardiovascular medication *No. (%)*	25 (2.48)
Mental health medication *No. (%)*	70 (6.96)
Mental health	

	Overall sample
Anxiety	
Yes (GAD7 score ≥10) *No. (%)*	165 (16.42)
Depression	
Yes (PHQ9 score ≥10) *No. (%)*	191 (19.02)
Post-Traumatic Stress Disorder	
Yes (PCL score ≥50) *No. (%)*	127 (12.66)
Deployment-related Post-Traumatic Growth (DPTGI)	
DPTGI Total score Median (IQR)	27 (16, 39)
DPTGI Appreciation of life (score range 0-9) Median (IQR)	5 (3, 7)
DPTGI Relating to others (score range 0-21) Median (IQR)	8 (4, 12)
DPTGI New possibilities (score range 0-15) Median (IQR)	7 (4, 10)
DPTGI Personal strength (score range 0-12) Median (IQR)	7 (4, 9)
DPTGI Spiritual change (score range 0-6) Median (IQR)	0 (0, 2)
Time in months between ADVANCE assessment and completing DPTGI Median (IQR)	0 (0, 12.65)
Haemodynamic functioning	
Heart rate (BPM) Median (IQR) *Normal resting heart rate 50-80BPM*	57.00 (51.67, 62.67)
Pulse wave velocity m/s Median (IQR)	7.77 (7.07, 8.77)

	Overall sample
Normal pulse wave velocity range: 4.2-9.4m/s	
Inflammation	
Median HsCRP mmol/l Median (IQR) *Normal range <1.0mmol/l*	0.90 (0.50, 1.77)
Cardiometabolic effects	
Diastolic blood pressure mmHg Median (IQR) *Normal diastolic blood pressure: <80mmHg*	73.00 (67.33, 79.00)
Systolic blood pressure mmHg Median (IQR) *Normal systolic blood pressure: <120mmHg*	129.00 (123.00, 137.00)
Total Cholesterol mg/dl Median (IQR) *Normal cholesterol: <200mg/dl*	189.48 (166.28, 216.55)
Triglycerides mg/dl Median (IQR) *Normal triglycerides: <150mg/dl*	97.43 (70.86, 141.71)
Triglycerides mg/dl Geometric mean (95% CI)	104.43 (100.97, 108.02)
High-Density Lipoproteins mg/dl Median (IQR) *Normal High-Density Lipoproteins: 40-60mg/dl*	50.27 (42.54, 58.01)
Low-Density Lipoproteins mg/dl Median (IQR) *Normal Low-Density Lipoproteins: <130mg/dl*	116.01 (96.68, 139.21)
HbA1C mg/dl Median (IQR) *Normal: <42mmol/mol*	34.00 (32.00, 36.00)
eGDR (Insulin resistance) Median (IQR) *Indicative of metabolic syndrome ≤8.77mg/kg/min*	9.82 (9.00, 10.38)

	Overall sample
Visceral Adipose Tissue cm^2 Median (IQR) *Normal: <100cm^2*	86.26 (67.96, 114.14)

Acronyms: CI Confidence Interval; DPTGI Deployment-related Post-Traumatic Growth Inventory; eGDR Estimated Glucose Disposal Rate; GAD Generalised Anxiety Disorder; IQR Interquartile Range; PCL Post-traumatic stress disorder Checklist; PHQ Patient Health Questionnaire

CHAPTER 6 TABLE 2: ROBUST REGRESSION COEFFICIENTS FOR POST-TRAUMATIC GROWTH FACTORS ON CARDIOVASCULAR RISK OUTCOMES WITH LINEAR RELATIONSHIPS

	Post-traumatic growth factor	**Model 1* coefficient (95% bias-corrected CI)**	**Model 2** coefficient (95% bias-corrected CI)**	**Model 3*** coefficient (95% bias-corrected CI)**
Diastolic blood pressure	Appreciation of life† (score range 0-9)	-0.335 (-0.558, -0.102)	-0.286 (-0.501, -0.032)	-0.425 (-0.669, -0.159)
	Spiritual change† (score range 0-6)	0.347 (-0.027, 0.756)	0.352 (-0.026, 0.724)	0.380 (-0.012, 0.742)
HbA1C	Spiritual change (score range 0-6)	0.182 (0.051, 0.310)	0.178 (0.058, 0.298)	0.149 (0.011, 0.279)
High-Density Lipoproteins	Appreciation of life (score range 0-9)	0.629 (0.286, 0.972)	0.423 (0.073, 0.804)	0.598 (0.189, 1.035)
	New possibilities (score range 0-15)	-0.491 (-0.736, -0.264)	-0.359 (-0.617, -0.108)	-0.606 (-0.901, -0.302)
Estimated Glucose Disposal Rate (Insulin Resistance)	Relating to others (score range 0-21)	0.007 (-0.004, 0.183)	0.007 (-0.003, 0.019)	0.005 (-0.008, 0.018)
	Spiritual change (score range 0-6)	-0.004 (-0.041, 0.035)	-0.000 (-0.039, 0.033)	0.002 (-0.363, 0.399)

	Post-traumatic growth factor	**Model 1* coefficient (95% bias-corrected CI)**	**Model 2** coefficient (95% bias-corrected CI)**	**Model 3*** coefficient (95% bias-corrected CI)**
Low-Density Lipoproteins	Personal strength (score range 0-12)	-0.810 (-1.402, -0.199)	-0.577 (-1.205, -0.004)	-0.680 (-1.460, 0.046)
Total cholesterol	Relating to others† (score range 0-21)	-0.656 (-1.146, -0.156)	-0.544 (-1.029, -0.093)	-0.584 (-1.168, -0.045)
	Spiritual change† (score range 0-6)	1.816 (0.102, 3.569)	1.448 (-0.288, 3.329)	1.534 (-0.502, 3.443)
Triglycerides††	Appreciation of life (score range 0-9)	0.979 (0.967, 0.991)	0.981 (0.969, 0.993)	0.982 (0.966, 0.995)
Visceral adipose tissue	New possibilities (score range 0-15)	-0.168 (-0.673, 0.417)	-0.111 (-0.651, 0.436)	-0.057 (-0.605, 0.509)

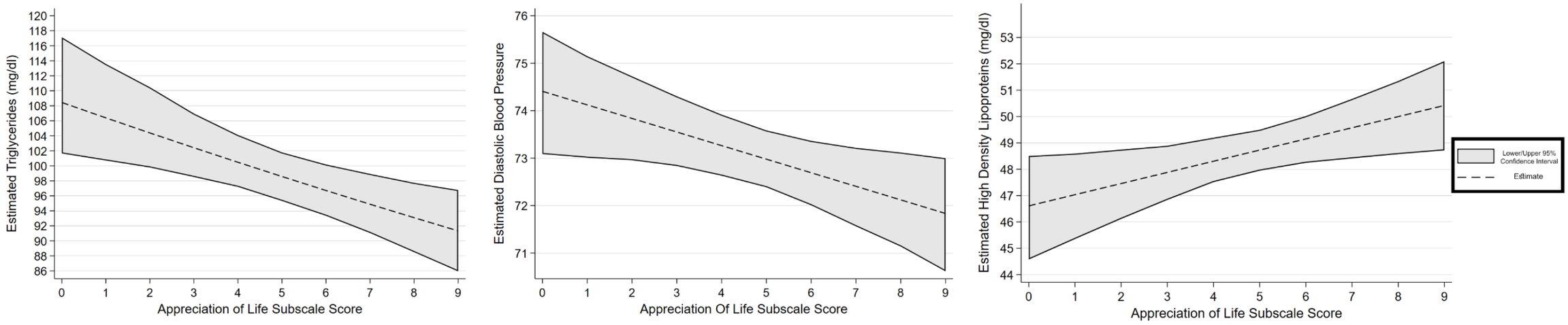
*Univariable model including PTG subscale score only

**Model including PTG subscale score and confounders (age at assessment, combat injury, medication use and socioeconomic status).

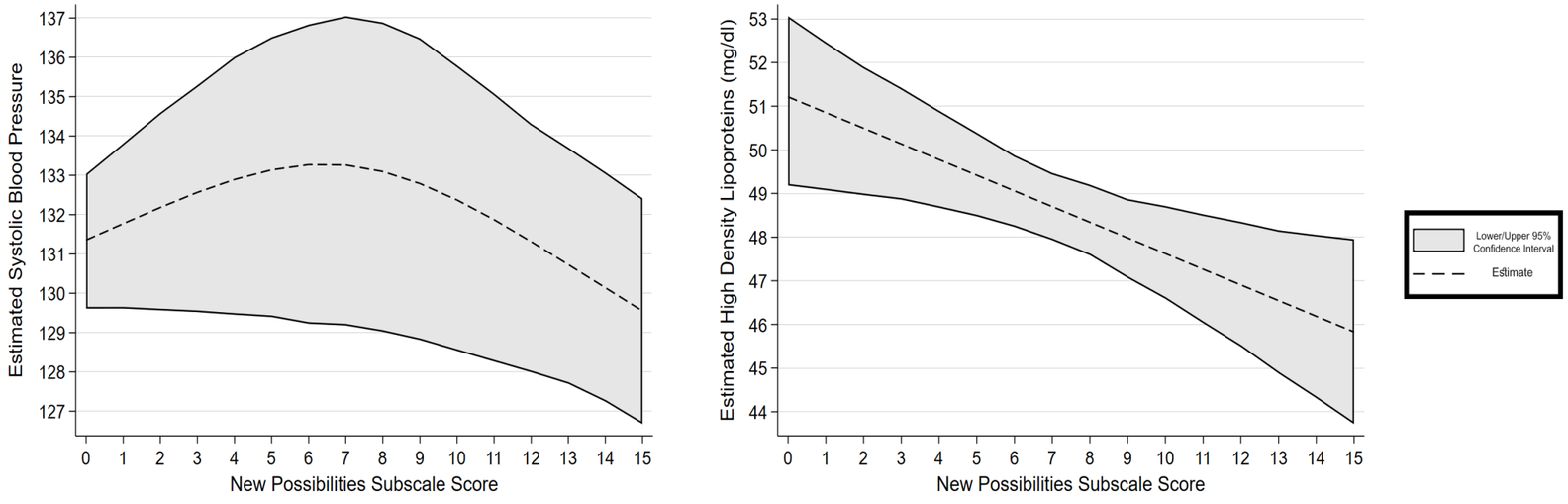
***Model including PTG subscale score and confounders (age at assessment, combat injury, medication use, socioeconomic status). Excludes those meeting threshold scores for probable anxiety, depression or PTSD).

	Post-traumatic growth factor	**Model 1* coefficient (95% bias-corrected CI)**	**Model 2** coefficient (95% bias-corrected CI)**	**Model 3*** coefficient (95% bias-corrected CI)**
†Both PTG subscale scores are included in a single model. ††Regression model was conducted on log-transformed triglycerides and exponentiated coefficients, reflecting percentage change in geometric mean, are reported here.				

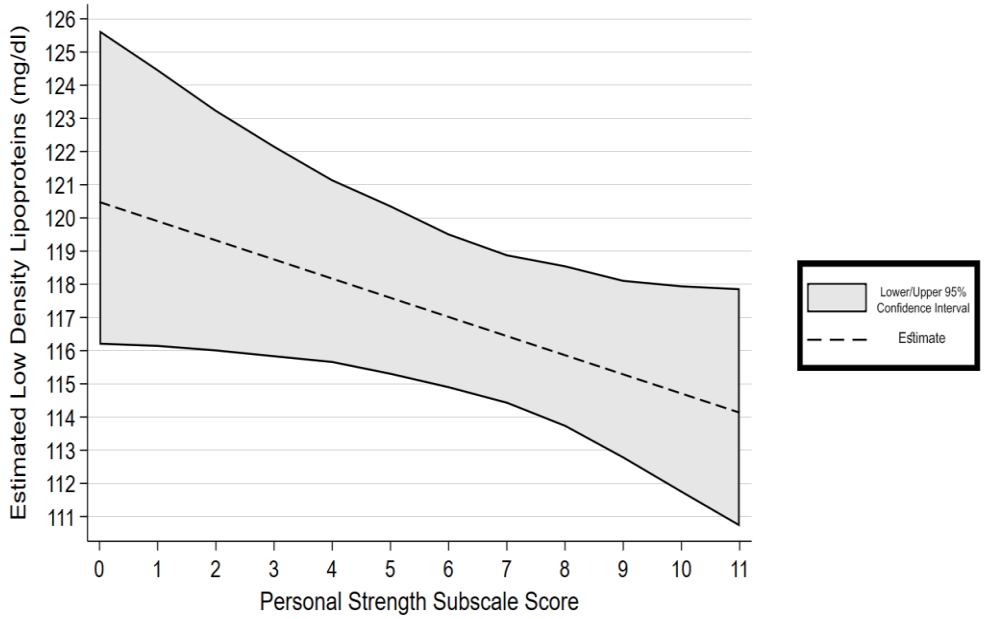
CHAPTER 6 FIGURE 1: ESTIMATED MARGINAL EFFECTS OF THE PTG FACTOR APPRECIATION OF LIFE ASSOCIATED WITH CARDIOVASCULAR RISK OUTCOMES, CONFIRMED IN ROBUST REGRESSION MODEL



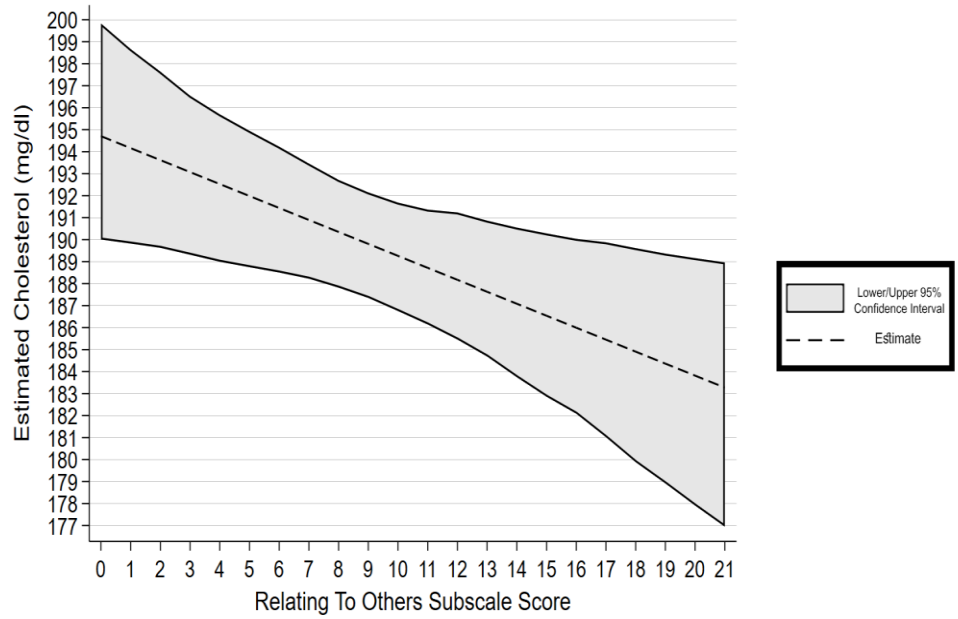
CHAPTER 6 FIGURE 2: ESTIMATED MARGINAL EFFECTS OF THE PTG FACTOR NEW POSSIBILITIES ASSOCIATED WITH CARDIOVASCULAR RISK OUTCOMES, CONFIRMED IN ROBUST REGRESSION MODEL



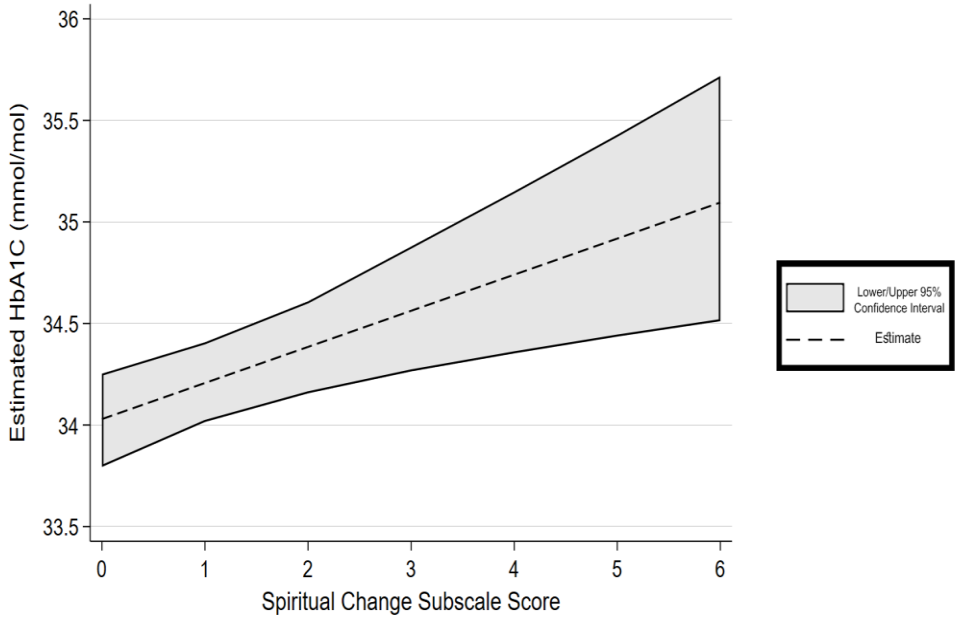
CHAPTER 6 FIGURE 3: ESTIMATED MARGINAL EFFECTS OF THE PTG FACTOR PERSONAL STRENGTH ASSOCIATED WITH LOW-DENSITY LIPOPROTEINS, CONFIRMED IN ROBUST REGRESSION MODEL



CHAPTER 6 FIGURE 4: ESTIMATED MARGINAL EFFECTS OF THE PTG FACTOR RELATING TO OTHERS ASSOCIATED WITH TOTAL CHOLESTEROL LEVELS, CONFIRMED IN ROBUST REGRESSION MODEL



CHAPTER 6 FIGURE 5: ESTIMATED MARGINAL EFFECTS OF THE PTG FACTOR SPIRITUAL CHANGE ASSOCIATED WITH HBA1C, CONFIRMED IN ROBUST REGRESSION MODEL



Discussion

In this study we hypothesised that factors of PTG would be associated with a better cardiovascular risk profile in the ADVANCE study cohort. We found that factors of PTG were associated with cardiometabolic effects and haemodynamic functioning but were not associated with inflammation (specifically inflammatory marker HsCRP). Our hypothesis was supported by our observations that the majority of factors of PTG were associated with better cardiovascular risk indicators. Robust regression models confirmed an association between greater scores on the AOL factor with decreased diastolic blood pressure, increased HDL and decreased triglyceride levels. Greater scores on the PS factor were associated with lower levels of LDL. Greater scores on the RTO factor were associated with lower total cholesterol levels. However, our hypothesis was also partially rejected as there were also associations between PTG and worse cardiovascular risk indicators. Greater scores on the NP factor were associated with decreased HDL and a non-linear relationship with systolic blood

pressure. Greater scores on the SC factor were associated with increased $HbA1_C$. The strength of all associations between PTG factors and cardiovascular risk indicators were small to modest.

Positive psychological constructs are associated with greater quality of allostatic and restorative processes, most likely through health behaviours such as physical activity, diet and sleep (8-10). These constructs, including PTG, are also associated with reductions in poor mental health outcomes, which themselves cause stress-related issues with physiological systems (5, 7). It is of note that almost all associations between PTG and cardiovascular risk outcomes were present even in the absence of participants with probable mental illness as observed in model three of our analysis which excluded those with probable depression, anxiety and PTSD. This suggests that these positive psychological outcomes are associated with cardiovascular health even amongst those with relatively good psychological well-being, supporting evidence that measurement of PTG is not simply measuring the absence of deleterious mental health constructs. AOL, PS and RTO were all associated with positive cardiovascular risk indicators. It is likely that there is significant overlap between positive psychological constructs such as gratitude, optimism, and factors of PTG, to the point whereby they may have equivocal effects on physiological health (47, 48), though it was beyond the scope of this study to investigate this. The distinction between these positive psychological phenomena with PTG is the perception of this growth being attributable to a trauma, in our case exposure to a warzone or sustaining a battlefield injury in Afghanistan. Interventions that are shown to increase any of these positive psychological constructs (6, 14-16) will theoretically have positive physiological effects on cardiovascular health, though longitudinal research would be needed to confirm this effect.

Spirituality and religiousness are generally perceived to be protective factors in cardiovascular disease. However, a meta-analysis investigating the physiological markers

associated with religiosity/spirituality also reported that diabetic risk markers including diabetes status, insulin resistance and fasting blood glucose were positively associated with religiosity/spirituality (49). In our study, SC was associated with worse cardiometabolic effects, specifically greater levels of $HbA1_C$, and limited evidence was also noted for associations with greater insulin resistance and higher total cholesterol levels. It could be that those who experienced SC were more likely to come from demographics at higher risk of cardiovascular disease, such as lower socioeconomic status (50), though further investigation is required to understand the mechanisms behind this relationship.

The NP factor was associated with lower levels of HDL cholesterol, which is generally considered as 'good' cholesterol. This factor includes items such as developing new interests, being able to make changes when necessary, seeing new opportunities, establishing new paths and perceiving those paths/options to be better than prior to the trauma. It is plausible that establishing new hobbies or interests could be correlated with increased opportunities to drink alcohol or eating at social events, though no research appears to exist on this link. On the other hand, it is also plausible that persons experiencing a large amount of growth on the NP factor might engage in more physically active hobbies, such as sports, or home cooking/positive changes to diet. This might explain the limited evidence observed for an association between NP and lower visceral adipose tissue (supplementary materials 5), though this was not confirmed by robust regression modelling. Experiencing greater growth on the NP subscale might be associated with both a mixture of poorer and better lifestyle factors. Future research would benefit from establishing whether there are differences in lifestyle factors such as diet, physical activity, and alcohol use/smoking/drug use between the factors of PTG.

Strengths of the study include investigation of a range of cardiovascular health indicators, a reasonably large sample size and use of best-practice statistical methodology for variable

selection (23, 24). However, this study also has a number of limitations. These results are based on cross-sectional analyses, therefore causation cannot be inferred. Methodologically, the variable selection procedures used in this paper were based on linear regression models including and excluding residual outliers. Due to the presence of these outliers, robust regression models were used to confirm associations selected by variable selection procedures. Unfortunately, it is not currently possible to conduct variable selection procedures using the robust regression methodology, which led to some PTG factors being selected but not confirmed by robust regression modelling. Whilst the majority of the ADVANCE cohort completed the DPTGI on the day of their assessment, a portion of the sample reported PTG over a year after their appointment. Missing data required the use of two-way imputation at an item level for the DPTGI. PTG was defined as specifically growth relating to any military deployments to Iraq/Afghanistan, which would not acknowledge PTG relating to any other traumatic event, which could confound associations in this study. It is likely that factors such as alcohol use, smoking and physical exercise mediate the associations observed in our study. Mediation analysis was beyond the scope of this current paper. The sample was limited to only male personnel, and findings may not translate to the female experience of PTG. Finally, whilst the five factors of PTG have been validated amongst a range of demographics including military/veterans (3), co-dependence was noted between some factors in our variable selection procedures, and questions exist regarding the distinctness of the factors from one another (51). It is possible that a more parsimonious understanding of PTG might be more beneficial to understanding the impact of PTG on physical health.

PTG is associated with mostly beneficial cardiometabolic effects and haemodynamic functioning, however associations with worse cardiovascular risk indicators are also noted. PTG is not associated with inflammation (specifically marker HsCRP). Further investigation

is required to understand why aspects of PTG are associated with both positive and negative cardiovascular functioning, and to understand whether the associations observed translate to changes in a person's cardiovascular risk profile in the long-term. Investigation into interventions that elicit aspects of positive psychological thriving and assess their impact on long-term cardiovascular risk is encouraged.

Declaration of interest statement

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Data availability statement

Given the sensitive nature of the participants, data have not been made widely available. Requests for data will be considered on a case-by-case basis and subject to UK Ministry of Defence clearance.

Key messages

Evidence before this study:

- Limited research has examined the association between PTG and cardiovascular health, however the broader literature on psychological thriving suggests that positive psychological constructs (e.g. optimism) are associated with better cardiovascular health.

Evidence from this study:

- Multiple factors of PTG were associated with beneficial cardiovascular risk profiles, however certain factors, namely new possibilities and spiritual change, were associated with some negative cardiovascular risk profiles.
- Factors of PTG were associated with cardiometabolic effects and haemodynamic functioning. These include associations between appreciation of life with lower diastolic blood pressure, greater High-Density lipoprotein levels (good cholesterol) and lower triglyceride levels; new possibilities with lower High-Density lipoprotein levels and a non-linear relationship with systolic blood pressure; personal strength with lower Low-Density lipoprotein levels (bad cholesterol); relating to others with total cholesterol levels, and spiritual change with higher $HbA1_{C.}$
- Associations between factors of PTG and cardiovascular health were present even in the absence of mental illness, indicating that PTG is associated with mostly beneficial cardiovascular functioning even when compared to those with moderate mental health.

Strengths of the study:

- Strengths include a relatively large sample size, the assessment of a range of cardiovascular risk factors and a rigorous variable selection procedure, alongside the use of bootstrapping and robust regression modelling.

Limitations of the study:

- 27.0% of participants completed the DPTGI >12 months after their ADVANCE study appointment, meaning there is a time disparity between the measure of PTG and cardiovascular health indicators.
- Lifestyle factors likely mediated associations between factors of PTG and cardiovascular health but were out of scope for this analysis.

- Co-dependence was noted between some factors, which might represent an indistinct nature between some of the factors of PTG. A more parsimonious understanding of PTG may be more beneficial to the scientific community.

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Discussion

Recommendations for future research, clinical implications and additional discussion of the analysis conducted in this thesis.

Overview

In this chapter, I will consider the results of the investigations conducted to address each of the aims of this thesis and provide additional discussion points beyond those already explored in chapters three-six, broken down by the thesis aims.

Rates of mental illness in combat injured personnel (chapter three)

Aim 1.1 Compare the rates of PTSD, depression, anxiety and mental health multimorbidity between injured and uninjured groups of Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).

Aim 1.2 Investigate whether subgroups of the injured group, specifically those who sustained an amputation injury and non-amputation injury, exhibit differences in rates of these outcomes.

The ADVANCE cohort study offers some of the best insights to date into the mental health consequences of combat injury. Previous studies have mostly focussed on US injured personnel, and often used comparison groups of other injured personnel (e.g. comparing those with genitourinary injuries to those who sustained non-genitourinary injuries) (1) without comparison to an uninjured group who would have similar deployment experience sans combat injury. Results from this thesis suggest that UK military personnel sustaining a combat injury had a greater likelihood of reporting probable PTSD, depression, anxiety and mental health multimorbidity compared to UK military personnel who were uninjured. However, this relationship was mostly attributable to the non-amputation injury subgroup. Those who sustained an amputation injury had no significant/minimal differences in mental health outcomes compared to the uninjured comparison group and significantly less compared to the non-amputation injury subgroup.

The study's strengths lie in the sampling of a frequency-matched uninjured group from which to draw a suitable comparison. By doing so, we can more confidently attribute mental health outcomes to the experience of combat injury by assessing two groups that were deployed to Afghanistan in similar roles, at similar times, but one group sustained a combat injury and the other did not. Bootstrapping the analyses allowed for a reliable statistical method for generating more precise confidence intervals. The study of mental health multimorbidity in addition to PTSD, depression and anxiety alone was important as it confirms what is seen in the wider literature; PTSD is a heterogenous disorder with high comorbidity (2-4). Finally, by

breaking down the overall combat injured group into amputation and non-amputation injuries, I was also able to investigate and discuss injury-specific mental health outcomes.

In chapter three (pg. 185-187), I discussed the results of my study in the context of the differences between US and UK reported rates of mental illness amongst physically injured military personnel, including specific discussion of amputation injuries, and media representations of those injured in combat, including a potential hierarchy of wounding. Implications for clinical practice including discussion of increased assessment of mental health amongst serving and veteran patients who deployed to Afghanistan and the increased psychological burden noted through multimorbidity amongst this cohort were also discussed. Below, I further discuss appearance altering injuries and perception of body image, cultural identity and current perceptions of heroism in war, possible mediating and moderating factors between combat injury and mental illness, mild/-Traumatic Brain Injury (TBI) and the Polytrauma Clinical Triad (PCT), the longer-term health of military personnel who sustained an amputation injury and the system to classify injury adopted in this thesis, along with additional clinical/policy implications of my work.

Perception of body image and mental health

The nuance of appearance altering injuries was not investigated as part of this thesis, as broader classification categories of amputation injury and non-amputation injury were employed. However, combat injury can range from anywhere between soft tissue lacerations to amputation, and even injuries such as lacerations might affect appearance. Amongst UK military personnel with appearance altering injuries, psychological distress has been reported with regards to the persons' alteration in self-concept following their injury and new appearance (5). Differences in the lived experiences of appearance altering injuries between those who experienced combat injuries versus training-related injuries were noted, which gives additional evidence towards a hierarchy of wounding already discussed in chapter three (pg. 185-187). Additionally, resilience and optimism were noted amongst some of those who experienced appearance-altering injuries, which could mean PTG is prevalent amongst this group. The perceived impact of visibility of injuries and social identity around combat-injury status will be explored in a future ADVANCE follow-up.

Cultural identity

I have discussed a potential hierarchy of wounding among those with a combat injury (chapter 3 pg. 185-187), however I have not discussed the intersectional nature of identifying as an injured Armed Forces serving personnel/veteran and current cultural discourse on

heroism. Cultural perception of wars, fatalities and injuries has changed considerably over the last 100 years, with recent generations increasingly having "less of an appetite" for war and military interventions (6). The perception of heroic actions by the West has also shifted. "The archetypal dimensions of war—legends of heroic deeds, divine mentoring of the warrior inspired by elders, and battle conditions where these patterns could be lived out sufficiently to shape the soul—have been handed down through generations to our present day. Yet modern conditions make the realization of these ancient and proven archetypes anachronistic, if not impossible. In modern war, combatants cannot become larger-than-life heroes." ((6), pg.77)). Consequently, a shift in focus has been made by the UK media with a focus on the experiences of UK veterans post-deployment. These stories tend to focus on either overly negative experiences, such as a focus on stories where veterans are portrayed as 'mad, bad or sad' or where the wounded warrior faces difficulties in adjustment to life after combat injury, or overly positive experiences, such as a focus on current charitable deeds or overcoming adversity/experiencing growth from what they endured as part of war (7-9).

The INVICTUS games, an Olympic style set of competitive games held by injured (physically or psychologically) veterans drawn from 23 different countries, have gained increasing positive attention from the UK population. Over 1.9 million people tuned in to the latest INVICTUS 2020 competition (10), held in 2022 due to COVID-19, and it is widely celebrated as a means for providing military veterans with injuries a sense of purpose, identity and a platform from which to be seen in a positive light by the general population (11, 12). The INVICTUS games pay tribute to ones' military career and provides hero status not necessarily based on their actions during war/service but for their ability to overcome the physical and psychological challenges of rehabilitation (13). It is likely that there is a mediating effect between sustaining a combat injury and subsequent mental illness based on one's ability to rehabilitate and be perceived as 'overcoming' one's injury. For example, those who are able to participate in sporting events that the INVICTUS games offer are likely to have important psychological benefits associated with that participation (14, 15). Those who are not able to participate in physical activities linked to sport or sporting events such as INVICTUS, either due to pain, severity of mental illness or the nature of their injury, may not benefit from such cultural identification of heroism (in terms of the definition of overcoming adversity) which may be to the detriment of their mental health (16). It is also unclear what may happen to the mental health of individuals who are unable to continue participation in

such events as age-related conditions become more prevalent, e.g. pain, reductions in mobility (17-19).

Mediating and moderating factors

An association was observed between sustaining a combat injury and experiencing probable mental illness, though this was dependent on the type of combat injury sustained. There are several other likely mediating and moderating factors of this relationship that were not explored and may be partly or even fully responsible for the subsequent mental health outcomes. Noteworthy mediators include chronic pain, physical activity or sleep (Chapter 7 figure 1). Noteworthy moderating factors include perceived social support, childhood adversity, or therapeutic/charitable interventions (Chapter 7 figure 2).

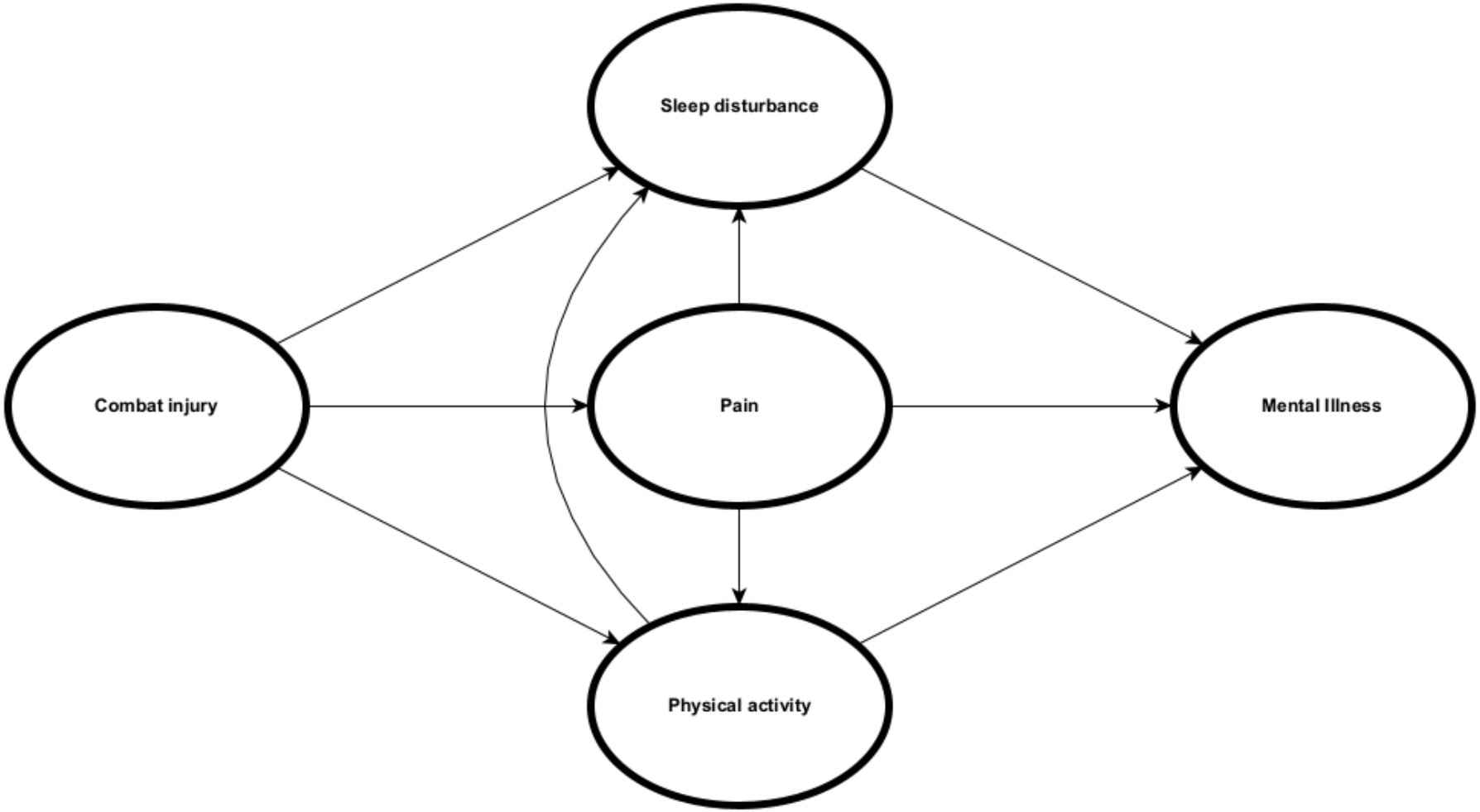
Physical activity has been observed to be associated with better mental health (20), including among veterans with a combat injury or PTSD (21). Whilst limited research has investigated the physical activity levels of those with a combat injury in the long-term, reductions in mobility associated with more severe combat injury is likely to reduce ones' ability to engage in physical activity (22, 23). It remains to be seen whether those who sustain a combat injury show increases in physical activity level (e.g. a person who experiences a combat injury and then goes on to become an athlete) or decreases in physical activity levels (e.g. a person stops or considerably reduces their physical activity levels compared to prior to the combat injury). Research into veterans in the US has suggested a U-shaped association between self-reported exercise frequency and probable PTSD, e.g. greater rates of no/very low exercise duration amongst veterans with PTSD and also greater rates of high/very high exercise duration compared to veterans without PTSD (24). Physical activity as a mediating factor between combat injury and mental illness was not explored in this thesis as it was beyond the scope of the analysis plan, though it would be possible to explore this within the ADVANCE cohort in the future.

Sleep has been identified as an independent risk factor for mental illness (25). Both short sleep duration (usually defined as <6 hours) and long sleep duration (usually defined as >8 hours) have been shown to be associated with poorer mental health (26). Sleep has a bidirectional relationship with poor mental health, by which poor mental health influences sleep duration/quality and sleep duration/quality influences mental health (25). Combat injury has been shown to be associated with reduced sleep duration and also poorer quality sleep (e.g. perceived satisfaction with the quality of your sleep) (27), though this does depend on

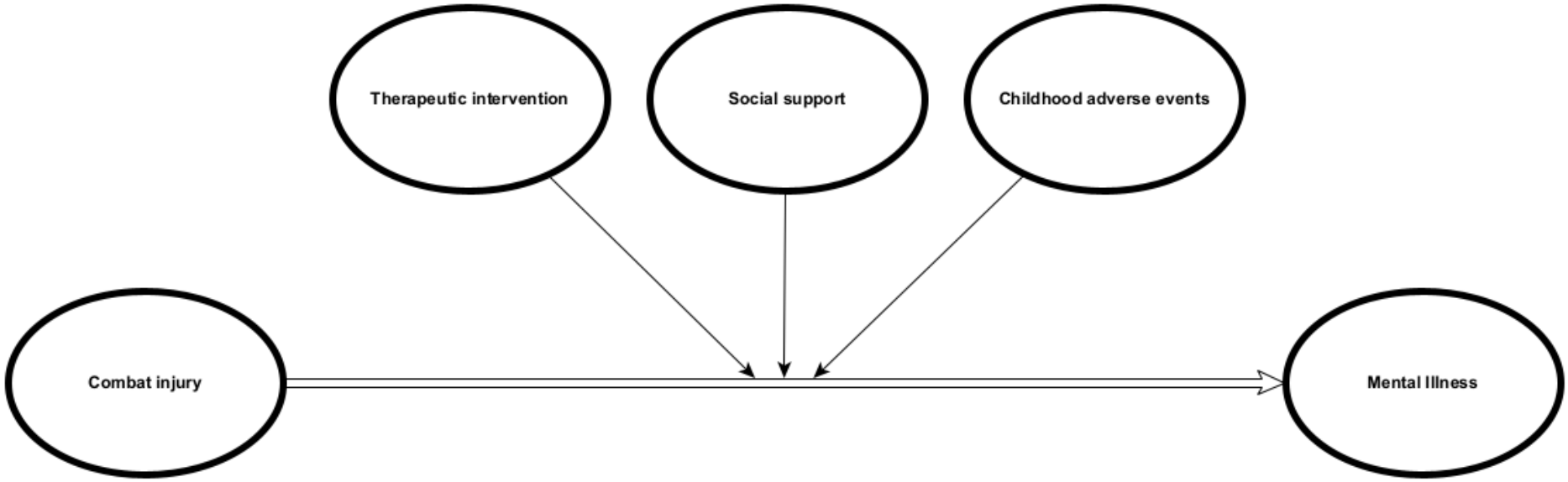
whether the person who sustained an injury additionally experienced PTSD, TBI or post-concussive symptoms (28).

Pain is associated with mental illness (29). Pain has a bidirectional relationship with poor mental health, by which increased pain is associated with increased rates of mental illness, and mental illness is associated with increased perception/reporting of pain severity (30). Combat injury may cause chronic pain, which in turn may increase the risk of mental illness (31). In chapter four (pg. 214-217), I discuss how moderate-extreme pain/discomfort was also associated with experiencing a large degree of PTG amongst those with a combat injury compared to the uninjured comparison group, indicating that pain has an even more complicated relationship with the broader spectrum of mental health than previously anticipated. The mediating, bidirectional nature of pain was not investigated as part of this thesis. Future research might look at the mediating factor of pain, and future follow-ups of the ADVANCE cohort will be well placed to investigate this complex association between pain and mental illness.

CHAPTER 7 FIGURE 1: POTENTIAL MEDIATING FACTORS BETWEEN COMBAT INJURY AND MENTAL ILLNESS



CHAPTER 7 FIGURE 2: POTENTIAL MODERATING FACTORS OF THE RELATIONSHIP BETWEEN COMBAT INJURY AND MENTAL ILLNESS



Social support is an independent protective factor against mental illness (32). Access to a good social support network might moderate the relationship between combat injury and mental illness (33). UK male personnel have been reported to access informal networks of support (e.g. family, friends) more often than UK female personnel (34). However, combat injured personnel might not experience this same level of support post-service due to difficulties in reintegration to civilian life as an injured person and alienation from military friends (35). Social support was not investigated as part of this analysis, but future follow-up assessments will be able to assess the impact of social support at baseline on reporting probable mental illness at follow-up.

Adverse childhood events have been recognised as significant predictors of poor mental well-being across the life course (36). UK military personnel who report greater rates of adverse childhood events have also been observed to report greater rates of mental and physical illness (37). It is possible that those who experienced greater rates of these adverse childhood events might have worse mental health outcomes if they sustained a combat injury and left service through medical discharge, though no research is currently available on this topic. Whilst details on adverse childhood events was collected as part of the IMPACTS questionnaire (Chapter 2 Supplementary Materials 1), this question was not addressed due to concerns that self-reported adverse childhood events have previously been shown to be reported inconsistently compared to actual events. This may be due to the fact that perception of adverse childhood events can be influenced by recall bias or factors such as age or current health (38, 39).

Access to therapeutic intervention or charitable services might moderate the relationship between combat injury and mental illness, as discussed in chapter three. The broader impact of interventions like these is worthy of additional investigation, as a proportion of the ADVANCE cohort would have had therapeutic interventions, help from military charities in various ways (e.g. funding for training, additional therapy, access to peer support networks) or taken part in sporting activities such as the INVICTUS games (14), or other adventurous activities (40). Unfortunately, details of these interventions were not gathered at baseline for the ADVANCE cohort. This data will be collected during a future follow-up for the ADVANCE cohort.

Traumatic Brain Injury (TBI), Mild-Traumatic Brain Injury (m-TBI) and the Polytrauma Clinical Triad (PCT)

M-/TBI are injuries that were prevalent in military personnel who sustained combat injuries during Iraq/Afghanistan. In a random sample of post 9/11 US veterans, the estimated rates of TBI were 17.3%, of whom the majority received the injury on deployment whilst exposed to blasts (33.1%) or hitting their head (31.7%) (41). History of TBI is associated with PTSD, sleep disturbance and depression (42). Rates of mTBI amongst UK Armed Forces personnel deployed to Iraq/Afghanistan were estimated to be 4.4% based on self-report data, and over double this amongst those who deployed in a combat role (9.5%) (43). The study also found that m-TBI was associated with PTSD (AOR 5.2, 95%CI 2.3, 11.4).

There is evidence of a trio of conditions, namely m-/TBI, pain and PTSD (otherwise known as PCT), being a prevalent and distinct injury profile. And has been observed amongst US military personnel deployed to Iraq/Afghanistan (44). No literature could be found on rates of PCT amongst UK military personnel deployed to Afghanistan, though amongst a treatment-seeking sample of veterans at a polytrauma network site in the US, 42.1% of patients were found to experience PCT (45). There is mixed evidence for whether this combination of disease has additive effects on suicidal ideation (46, 47) and sleep disturbance (48).

Neither TBI nor PCT were assessed as part of the work conducted in this thesis. Whilst it was noted as an important factor in the literature in regards to subsequent mental health (49) and cardiovascular health (50), the data on the nature and severity of head injuries was not available for the baseline dataset from the ADVANCE study to utilise at the time of writing this thesis, and indeed details regarding the severity of military head injuries are noted as lacking generally in the scientific literature (51). This data will be available for future follow-ups of the ADVANCE study. PCT in UK military personnel in particular is an under-researched area and warrants further investigation.

Long-term health

The ADVANCE study is the first study to investigate the link between sustaining a combat injury and long-term health, which at baseline was a median of seven years post injury. Whilst in my work, I have observed that those who sustain an amputation injury appear to have similar rates of mental illness to those who were deployed to Afghanistan and remained uninjured, this may not be the case as these participants age further. Age related pain (17), reduced mobility (18) and other complications of amputation that may worsen with age (19) could impact negatively on these military serving personnel/veterans' mental health.

As well as physical factors associated with aging, events in the world also have the potential to impact on the long-term mental health of this cohort. In 2021, the Taliban took power once again in Afghanistan. Prior to the takeover, UK military personnel who deployed to Afghanistan may have felt that their impact was positive/meaningful, and the sacrifices they or friends/colleagues made were worthwhile, which may have had a protective effect on their mental health (52, 53). These new developments may have UK military personnel questioning their involvement and ultimate impact on peace/stability in Afghanistan (54). It is unknown how these or other geopolitical developments e.g. the UK military assistance provided to Ukraine since the Russian invasion (55) will affect the well-being of UK military personnel who sustained life-changing injuries as a result of their deployments or even those uninjured. ADVANCE is a 20-year study and will be well-placed to monitor the well-being of the cohort and ask questions regarding their thoughts/feelings about the changing geopolitical landscape, both in Afghanistan and closer to home in Europe.

Classification of groups

The non-amputation injury subgroup was a difficult group to categorise in terms of injuries. The type of injuries (e.g. penetrating injury, fracture) and location of injury (e.g. head, upper limb) were insufficient in indicating severity of injury. New Injury Severity Score (NISS) was a primary indicator of severity of injury, however NISS was unsuitable to use as a method of comparison (e.g. high NISS versus low NISS) due to outliers. Amongst UK Naval personnel who sustained an injury in TELIC or HERRICK, higher NISS scores were generally reflective of likelihood to return to duty, though there were exceptions to this rule (56). For example, injuries resulting in sensory deprivation (e.g. hearing loss) and PTSD. In the ADVANCE cohort, similar exceptions to this rule were noted, whereby some individuals with relatively low NISS had high levels of functional impairment (e.g. limb loss) (see Chapter 2 Figure 8). Whilst all participants in the study required casualty evacuation to a UK hospital due to their injuries, there appears to be diverse post-injury experiences in these individuals, and injury severity scores at time of injury may not be predictive of long-term prognosis/quality of life (57).

Injuries observed in the ADVANCE cohort ranged in severity from lacerations to head injuries and limb loss. Often, participants experienced multiple types of injuries simultaneously. Body regions associated with injury were mostly similar between the amputation and non-amputation injury subgroups, with the exception of lower limb injuries, which were greater amongst the amputation injury subgroup (chapter 2 figure 7). As such, the

only method of classification deemed suitable was comparing subgroups of injured personnel with and without amputation injuries. This is a limitation of the work conducted in this thesis. Future studies of the ADVANCE cohort may benefit from a more distinct/detailed classification of the injured cohort. A network analysis of critically injured combat veterans from the US has identified patterns of injuries which contribute towards likelihood of mortality (58). Using these results, categories could be defined for the ADVANCE cohort based on patterns of injuries sustained with increased likelihood of initial mortality, which could form a basis for future investigations of the ADVANCE cohort.

Clinical/policy implications

Whilst ADVANCE will be looking to identify factors associated with lower rates of mental illness and psychological thriving (e.g. social support, therapeutic intervention) in the cohort and attempting to explain why those who sustained amputation injuries have better mental health outcomes, other clinical inferences can be made from the current data. In chapter three (pg. 185-187) I discussed the fact that both civilian and military clinicians would benefit from enquiring about mental health amongst those who served in recent conflicts, even if no obvious (visible) combat injury exists. Additionally, I discuss the high psychological burden noted in this cohort, which is generally associated with greater suicidality and lower quality of life (59). It is especially worth considering that whilst UK veterans do not have different rates of suicide to the general population, their risk of suicide is much greater in the under-25 years of age group (60), and there is an observed relationship between sustaining a combat injury and subsequent suicide attempt particularly amongst those with multiple mental health diagnoses in US veterans (61). It may be useful for clinicians to implement mental health interventions integrated into physical health rehabilitation/maintenance efforts. The UK Office for Veteran's Affairs (OVA) have set out a Veterans' Strategy Action Plan that includes greater signposting from general practitioners to veterans regarding veteran specific support provided by NHS England (62). This includes integrated plans to support the mental and physical health of veterans with and without service-related injuries. Strength training and cardiovascular training have been associated with better mental health, as well as increased mobility and lower physical comorbidity (16, 63). Integrating mental health components such as social support or mental health psychoeducation into these physical well-being interventions might be a socially acceptable (e.g. less stigmatising) way of treating mental illness. An added benefit of this approach would be that it would also minimise

factors associated with subsequent poor mental well-being (e.g. mobility, quality of life) that may become particularly important as the combat-injured cohort ages (17-19).

Recommendations for future research

As discussed in chapter three (pg. 185-187) and above, to break down and understand the relationship between combat injury and subsequent mental illness, researchers would benefit from investigating perception of body image, further scrutiny of the psychological burden of multimorbidity in those with amputation/non-amputation injuries, hierarchy of wounding, cultural identity and the specific outcomes of those with m-/TBI or PCT. Accounting for or investigating the effects of additional moderating/mediating factors between combat injury and mental illness would also be beneficial. Additionally, the OVA has launched a survey that covers topics such as loneliness and social isolation amongst veterans (64). Investigating whether the hierarchy of wounding and social identity around combat injury interact with loneliness and social isolation would be useful to understand the complex interplay of intersectional identities and support networks an injured service person/veteran has and how that might influence their mental health.

Experience of Post-Traumatic Growth in combat injured personnel and its mediating factors (chapter four)

Aim 2.1 Investigate PTG experienced as a result of deployment to Iraq/Afghanistan between injured and uninjured groups of Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).

Aim 2.2 Investigate whether subgroups of the injured group, specifically those who sustained an amputation injury and non-amputation injury, exhibit differences in rates of deployment related PTG.

Aim 2.3 Investigate whether depression, PTSD and pain mediate the relationship between combat injury and PTG.

In this study, we found that those who sustained a combat injury were more likely to report a large degree of PTG compared to the uninjured group. However, once again we find that the type of combat injury is important to consider. Those who sustained an amputation injury were more likely to report a large degree of PTG compared to the uninjured group, whereas the non-amputation injury group reported minimal differences compared to the uninjured group. Depression, PTSD and pain partially mediated this relationship, with a surprising finding that pain was associated with a greater likelihood of reporting a large degree of PTG.

The strengths of this study largely mimic those from the first aims of this thesis. The use of a frequency-matched uninjured group allows for greater confidence in the associations between combat injury and PTG. This study also uses GSEM, a strong statistical approach to mediation analysis and causal inference, further strengthened by bootstrapping of the confidence intervals. This study was, to the authors knowledge, the first to assess the mediating qualities of PTSD, depression and pain between combat injury and PTG. The statistical approach also took into account the non-linear association between PTSD and PTG.

In chapter four (pg. 214-217), I discussed the differences observed in rates of mental illness between those who sustained an amputation injury and those that sustained non-amputation injuries and the possibility that those with amputation injuries may have had greater or easier access to post-military-service therapeutic or charitable interventions that could have reduced mental illness symptoms and increased psychological thriving (PTG). I also discussed; the deployment, health and demographic factors known to be associated with PTG in UK military personnel who deployed to Iraq or Afghanistan, the link between pain and rumination as a potential explanation for the positive association observed between pain and PTG, and clinical implications of this work including potential interventions in high-risk groups that aim to promote psychological thriving following deployment or injury. In this chapter, I will additionally discuss the problems of deployment-specific PTG, the distinction between PTG and other aspects of psychological thriving, the relationship between PTSD and PTG, how a hierarchy of wounding might affect PTG and clinical implications of this research.

Deployment-related PTG

In this thesis, a deployment-related version of the PTGI was administered. The stem question was changed from “Indicate for each of the statements below the degree to which this change occurred in your life as a result of crisis” (65) to “Please read each statement and tell us whether you have changed for the better a result of ALL your deployments to Iraq/Afghanistan since 2002” (66). Due to this wording, specific perceived growth from deployment related experiences can be deduced. However, it also means that growth that may have been elicited from other crises/traumas is not measured and may confound investigated associations. For example, a person who does not perceive any PTG being elicited from their deployments to Iraq/Afghanistan, but does perceive growth from a trauma experienced in their personal life (e.g. car accident) would have been measured as having no/low PTG in this

thesis despite having PTG from other sources. This would have masked (i.e. reduced the statistical significance) the strength of the association between measured deployment-related PTG and cardiovascular functioning. As such, this is a limitation of the thesis.

Distinction between PTG and other aspects of psychological thriving

PTG is, by definition, psychological thriving following a trauma. Psychological thriving is the term used to describe positive psychological constructs such as emotional vitality, defined as a positive active engagement with the world, gratitude, optimism, positive affect, psychological mastery and PTG. The distinction between other aspects of psychological thriving and PTG may only be that PTG is elicited through experiencing trauma. Questions have been asked in the scientific community regarding the distinctness of the factors of PTG (67). Aspects of PTG such as appreciation of life, personal strength, relating to others and new possibilities may be functionally similar to broader constructs of psychological thriving such as gratitude, optimism, or positive affect (68). It would seem that investigation of these broader constructs of psychological thriving and their similarity to factors of PTG might be a future avenue of exploration, with the aim of achieving a more parsimonious understanding of positive psychology.

PTSD, PTG, pain and rumination

PTG and PTSD have a known curvilinear relationship (69). Total scores of the PCL-C were used to define PTSD caseness (PCL score 50+ indicated probable PTSD) and tertiled total scores of the DPTGI were used to define the rates of PTG (No/a low degree of PTG (scores 0-20), a moderate degree of PTG (scores 21-34) and a large degree of PTG (35-63)) for the first and second set of aims of this thesis. Further research may be conducted to elucidate the symptom-specific relationships between PTSD and PTG, especially considering the different associations noted between cardiovascular health and PTSD symptom clusters and factors of PTG observed in chapter 5 and 6. One study investigating Chinese young adults in the aftermath of a typhoon undertook network analysis to answer this question and found a series of eight PTSD/PTG symptoms that acted as ‘bridge’ symptoms between PTSD and PTG (e.g. symptoms that act as a link between concepts) (70). PTSD symptoms included intrusive thoughts, nightmares, emotional cue reactivity, physiological cue reactivity, hypervigilance, and self-destructive or reckless behaviour. PTG symptoms included changed priorities and stronger religious faith. These bridge symptoms suggest that rumination is the key factor that bridges the gap between PTSD and PTG. Considering in this thesis I also found that pain was associated with greater rates of PTG and hypothesised that pain main be associated with PTG

through rumination (pg. 215), rumination seems to be an underlying key cognitive process involved in the mental health of this cohort. Intrusive rumination, rumination that occurs in the form of automatic re-experiencing the thoughts/feelings/images relating to the trauma, is associated with increased mental illness (71), whereas deliberate rumination, an intentional thought process whereby one attempts to understand the meaning surrounding their experience of the trauma, is associated with psychological thriving (72). Further research on types of rumination and their relationship with PTSD, PTG, and pain is recommended. Additionally, considering PTSD and pain form part of the PCT, it would be of clinical importance to assess rumination in the context of PCT with the aim of reducing severity of symptoms for this highly comorbid condition.

Clinical/policy implications

In a review of the factors associated with PTG, experience-sharing and social support were identified as particular themes contributing to PTG (73). The review, alongside a qualitative study investigating UK veterans' experiences of PTG (74), suggested that "…it was not simply the presence of social support that contributed to PTG, but that the "support network" needed to have an in-depth knowledge of the individuals difficulties and trauma experiences (e.g. the spouse) in order to maximise growth" ((73), pg. 3). It is possible that UK military personnel might benefit from this support network or indeed be able to foster such a network more easily due to close-knit community within the Armed Forces, a culture of comradery and 'band of brothers' (75). This is especially true of those with an amputation injury, who would all experience similar difficulties and be able to relate to one another's experiences (e.g. prosthetics, phantom pain, mobility issues etc.). This may be less true for those who sustained non-amputation injuries, who would likely experience a more diverse range of difficulties as a result of their injuries, though may still benefit from support networks with shared deployment experiences.

A recent evaluation of the Armed Forces Covenant Fund Trust's 'Tackling Loneliness Programme' reports that the social support network a veteran had developed during their time in the military is at risk of being fractured during the transition from military to civilian life, and that interventions aiming to reduce loneliness and mend this fracture had extended benefits for the mental health of these individuals (76). The Australian government have a Coordinated Veterans' Care (CVC) social assistance program aiming to assist veterans who might feel disconnected/isolated from their community through access to ex-service organisations, activities and courses (77). Peer support network groups in the UK are

advertised through military charities such as Combat Stress, Help for Heroes and the Soldiers, Sailors, Airmen and Families Association (SSAFA). The UK Veterans' Mental Health Transition, Intervention and Liaison Service (TILS) also provides help with social support (78). Additionally, operation COURAGE, the NHS initiative designed to support the mental health needs of ex-serving personnel or servicemen currently transitioning to civilian life, can provide guidance in finding local peer support groups.

Historically, the Guinea Pig Club was a successful peer support group for wounded aircrew from World War II (79, 80). Formed in 1941, the group initially consisted of individuals with the shared experience of burn injuries, though this eventually expanded to other types of injuries too. Whilst in hospital for rehabilitation, patients were encouraged to interact with one another, the local townspeople as well as the clinicians at the hospital. The Guinea Pig Club continued to meet after the War/their rehabilitation and offered a sense of community to former patients. The spiritual successor to the Guinea Pig Club, now called the CASEVAC Club, started in 2017 and continues the traditions of the Guinea Pig Club, offering peer support to its members of wounded serving personnel and veterans. Accounts of rehabilitation at Headley Court continue to identify the importance of the peer support network from fellow Armed Forces personnel and more experienced prosthetics users alongside support from the clinical teams for those who sustained amputation injuries in particular (63). The CASEVAC Club and the Guinea Pig Club offer some insight into the benefits of establishing a community among injured Armed Forces personnel, starting as soon as rehabilitation care begins and continuing through and beyond the transition to civilian life. Learning from and officially evaluating such programs already in existence (including the INVICTUS games), as well as piloting programs that aim to connect combat injured personnel is recommended as an area of future investigation.

Recommendations for future research

As discussed in chapter four (pg. 214-217) and above, an investigation into the distinction of PTG compared to other constructs of psychological thriving, the inter-related domains between PTSD and PTG, deliberate and intrusive rumination as factors contributing to positive and negative mental health, and assessment of social support programs aimed at bringing those who sustained combat injuries together would be of interest to the scientific and military communities. Additionally, I have discussed factors around cultural identity and the potential for a hierarchy of wounding, whereby certain injury profiles might be perceived in a more beneficial light (e.g. combat injuries versus training injuries or obvious/visible

injuries versus less obvious/invisible injuries), which might be a protective factor against subsequent poor mental health outcomes. To my knowledge, no investigation has occurred into a hierarchy of wounding in the context of PTG and is recommended as a future avenue of investigation.

PTSD symptom clusters and CVD risk (chapter five)

> **Aim 3.1 Examine whether PTSD symptom clusters are associated with cardiovascular risk factors including inflammation, cardiometabolic effects and haemodynamic functioning in a cohort of injured/uninjured Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).**
> **Aim 3.2 Assess the relative importance of these symptom clusters via variable selection procedures and confirm results via robust regression modelling.**

In this study, I hypothesised that hyperarousal symptoms would best explain associations between PTSD symptoms and cardiovascular risk factors. I did find that PTSD symptom clusters were associated with cardiometabolic effects and haemodynamic functioning, but not inflammation. However, I found that multiple symptom clusters, rather than simply hyperarousal, best explained these associations.

The study's strengths include investigation into a comprehensive suite of cardiovascular risk indicators based on an a-priori knowledge base from the scientific literature in a relatively large sample size. Great lengths were taken to ensure the quality of this data, employing recommended techniques for data cleaning. Application of a rigorous set of variable selection procedures produced a model addressing model uncertainty and co-dependence between symptom clusters, robust to outliers in the residuals. Additionally, looking at symptom cluster severity, rather than simply presence or absence of PTSD, allows for a greater understanding of the potential psychological mechanisms by which PTSD elicits cardiovascular responses.

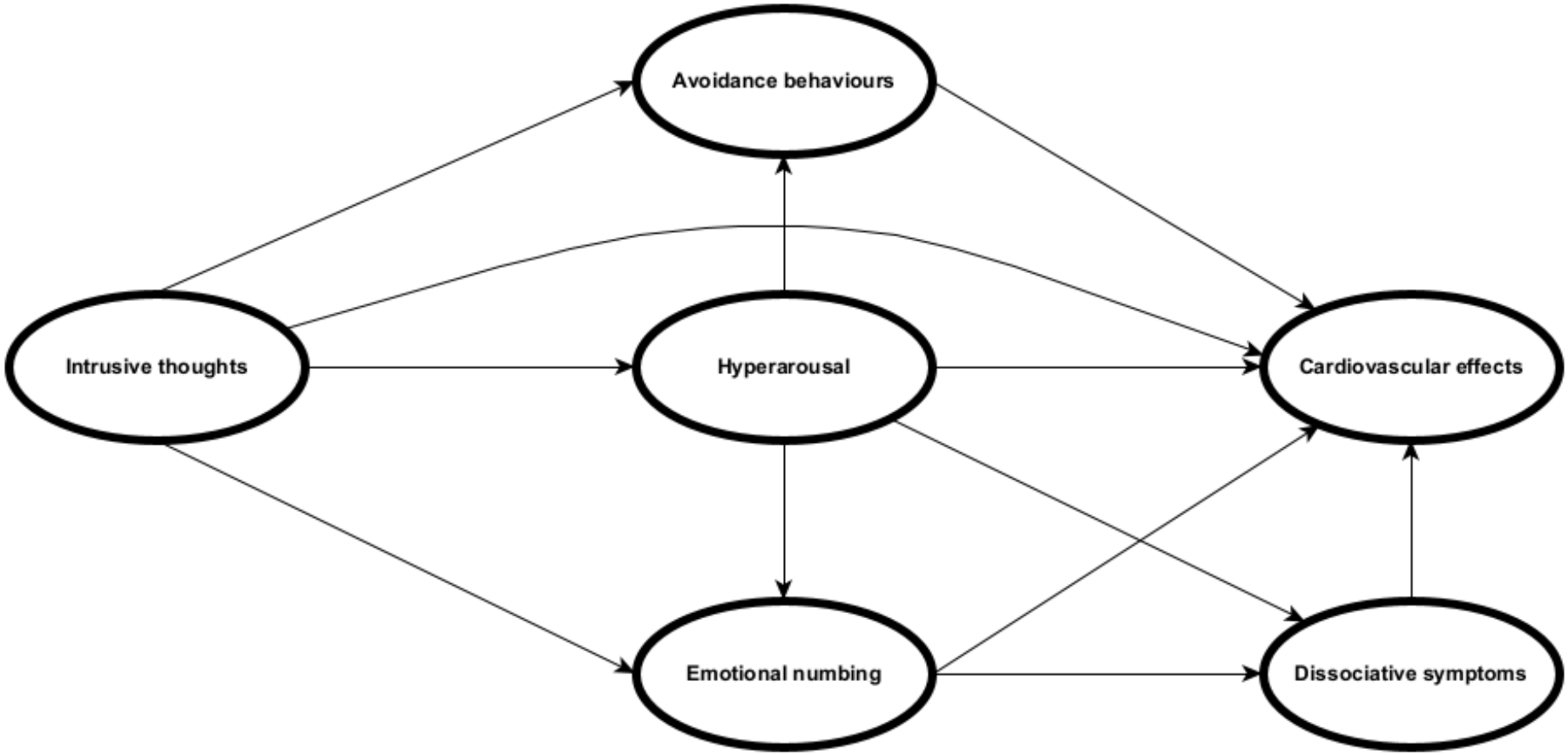
In chapter five, I discussed; the fact that dissociative symptoms may confound/mediate associations between PTSD and cardiovascular risk due to the different cardiovascular effects noted amongst those with the dissociative subtype of PTSD; the possibility that sustained over stimulation from hyperarousal symptoms may lead to depletion of cognitive resources and result in emotional numbing, which again may lead to different cardiovascular effects compared to the hyperarousal model; the proposed link between intrusive thoughts and subsequent hyperarousal events, the healthy warrior effect, and clinical implications including assessing for cardiovascular health amongst those with known PTSD and

implementing early monitoring strategies to mitigate the increased CVD risk noted in this population. In this section, I will discuss further the causal inferences of PTSD symptoms on cardiovascular functioning, implementation of early intervention strategies in those with PTSD, adding mental health to predictive models of CVD to improve accuracy, and the potential disconnect between academia and clinicians.

Causal inferences between PTSD symptom clusters and cardiovascular functioning

In chapter five, I discuss the likely causal relationship between experiencing intrusive thoughts and subsequent hyperarousal symptoms (pg. 247-252). It is likely that all four of the symptom clusters of PTSD have a causal, mechanistic relationship with intrusive thoughts. In Chapter 7 figure 3, I describe potential causal links between the four symptom clusters and cardiovascular effects. PTSD is characterised by symptoms of intrusive thoughts, whereby the person with PTSD re-experiences aspects of the trauma. From this initial re-experiencing symptom, the person may have a hyperarousal response (e.g. increased heart rate). To reduce the impact of these symptoms, the person may attempt to avoid certain situations, places or people that remind the person of the trauma to reduce the likelihood of re-experiencing (e.g. intrusive thoughts) or a hyperarousal response. As discussed in chapter five (pg. 247-252), emotional numbing is hypothesised as emotional/cognitive exhaustion from repeated exposure to hyperarousal symptoms (81-83). Additionally, this emotional numbing and repeated exposure to hyperarousal symptoms may lead to dissociative symptoms in some, with subsequently different cardiovascular effects as a result. A network analysis of combat veterans in the US has investigated the relationship between PTSD symptoms and found that flashbacks and getting emotionally upset by trauma reminders were the most central symptoms across all PTSD networks (central symptoms have a large number of connections in a network, so activation of central symptoms lead to activation of many other connecting symptoms in the network (84)), and most interestingly, that all re-experiencing symptoms (e.g. intrusive thoughts) had the strongest associations with other symptoms in the network (85). Future research using the first follow-up assessment for ADVANCE would be able to assess whether this hypothesised causal relationship between the PTSD symptom clusters and cardiovascular effects is supported and assess the direct and indirect effects of this relationship.

CHAPTER 7 FIGURE 3: CAUSAL DIAGRAM OF PTSD SYMPTOM CLUSTERS, DISSOCIATIVE SYMPTOMS AND CARDIOVASCULAR EFFECTS



Clinical/policy implications

Early intervention strategies have been identified as an important avenue for clinical intervention to either delay or prevent further progression of CVD (86). Prediction of those who would benefit from such interventions have generally focussed on clinical or lifestyle factors (87). As seen in this thesis, cardiovascular risk is present in those with PTSD symptoms despite the cohort being relatively young. Models of prediction should include mental health aspects to help identify those who would benefit most from early intervention. Early research into the use of predictive models of cardiovascular risk including mental health data have yielded positive results (88). Strategies to prevent CVD have been advised to contain psychosocial assessment including CMD, stress, quality of life, as well as alcohol and substance misuse based on the British Association for Cardiovascular Prevention and Rehabilitation standards and core components for cardiovascular prevention and rehabilitation (89). Results from this thesis suggest that, for those exposed to potentially traumatic events, assessment of PTSD symptoms could be a useful addition to this model, especially amongst military personnel exposed to combat and/or combat injury.

Whilst the association between PTSD and CVD is well known amongst the academic community, there may be a disconnect between this knowledge and the clinical community (e.g. doctors, general practitioners, mental health practitioners). This is especially true of the fact that the relationship between PTSD and cardiovascular risk is present even amongst the relatively young (median age 33), a group that would not traditionally be at risk in the absence of other risk factors for CVD (e.g. diabetes), as discussed in chapter one (pg. 51-81) and chapter five (pg.247-252). Currently there are only eight Academic Health Science Centres (AHSCs) in the UK. AHSCs aim to transfer academic learning to NHS organisations to ensure academic discoveries translate to patient care (90). Adding this up to date learning regarding PTSD in injured/uninjured veterans to the learning materials from the Royal College of General Practitioners is recommended (91). Increased work to ensure that awareness of the link between mental health and cardiovascular health has the potential to positively impact the health of those with mental illnesses, especially for military personnel injured in combat who might already be at increased risk due to their injuries (92).

Recommendations for future research

As discussed in chapter five (pg. 247-252) and above; the effect of dissociative symptoms alongside the core PTSD symptom clusters; the potential clinical implications of PTSD symptom clusters being associated with cardiovascular risk as early indicators of later

worsening cardiovascular health; the implementation of mental health assessment in general hospital settings; the causal inferences between symptom clusters and the potential for avoidance behaviours; emotional numbing and hyperarousal to be mediators of the relationship between intrusive thoughts/re-experiencing and cardiovascular health and the assessment of mental health components within physical health interventions for those identified as having greater cardiovascular risk in an early intervention setting would be recommended for future research. Furthermore, extending research into the addition of mental health variables in prediction modelling techniques to identify individuals who would benefit from early intervention strategies to reduce the risk of developing CVD would be beneficial (88).

PTG symptom clusters and CVD risk (chapter six)

> **Aim 4.1 Examine whether factors of PTG will be associated with better cardiovascular health indicators including inflammation, cardiometabolic effects and haemodynamic functioning in a cohort of injured/uninjured Afghanistan-deployed UK Armed Forces personnel (the ADVANCE Cohort).**
> **Aim 4.2 Assess the relative importance of the factors of PTG in these associations via variable selection procedures and confirm results via robust regression modelling.**

In this thesis, I hypothesised that the five factors of PTG would be associated with better cardiovascular health. I found that factors of PTG were associated with positive indicators of cardiovascular health including cardiometabolic effects and haemodynamic functioning, but not inflammation. However, some factors, including new possibilities and spiritual change, were also associated with poorer cardiovascular health.

Strengths of this study largely mimic those of the third aim of this thesis. The study benefits from a relatively large sample size of UK Armed Forces personnel from which a comprehensive suite of cardiovascular measures were taken. Rigorous variable selection procedures were employed and additional steps were used to address model uncertainty and potential co-dependence between factors of PTG. Factors of PTG were investigated on continuous subscales instead of just the absence or presence of a large degree of PTG, which allows for greater scrutiny of the psychological mechanisms by which PTG might elicit a cardiovascular response. Additionally, models were repeated excluding those with mental

illness, which supports the idea that PTG is measuring more than just the absence of mental illness.

In chapter six (pg. 282-287), I discussed the fact that associations between factors of PTG and cardiovascular health were present even in the absence of mental illness, the known associations between spirituality and poorer fasting blood glucose, and the possible reasons why the PTG factor new possibilities might reflect lifestyle factors with diverse cardiovascular responses. In this chapter, I will discuss further the distinction of PTG from other constructs of psychological thriving, measurement of retrospective versus actual growth and implementation of positive psychology elements to early intervention strategies to reduce risk of/ delay the development of CVD.

Psychological thriving and cardiovascular health

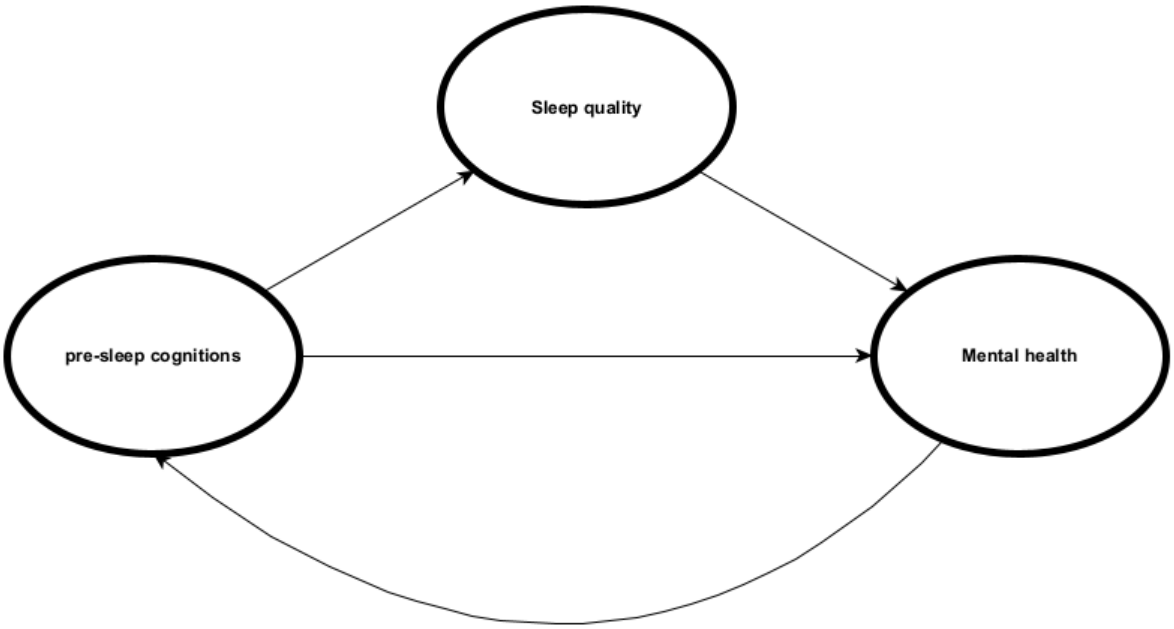
The focus of much scientific endeavour over the past century has been to understand the pathology of mental illness, and it is only in recent years that the broader spectrum of positive psychology has been investigated with any rigour. As such, the evidence for physical health consequences of PTG, whilst present, is limited in the wider literature. The evidence for associations between psychological thriving and cardiovascular health though, are more well researched, and it is unlikely that there are differences between other aspects of psychological thriving and PTG in the underlying mechanisms by which they affect cardiovascular health.

Psychological thriving has been shown to be associated with lower rates of CVD and mortality from CVD in the general population (93, 94). The most well-researched construct within the spectrum of psychological thriving is optimism. Optimism has been associated with lower rates of CVD, lower mortality from CVD and better physiological functioning (95-97). Emotional vitality, emotional regulation and a positive sense of well-being alongside optimism have been shown to be a protective factor against coronary heart disease (98), including in a prospective study of middle aged British civil servants (96). Psychological mastery, defined as the ability to control negative emotions, is associated with a decreased risk of CVD mortality, with a greater effect apparent within those with a lower number of comorbid cardiovascular risk factors (99).

Psychological thriving is theorised to affect physiology through increases in restorative processes, including sleep, physical activity, diet and perceived social support, as well as decreases in deleterious processes, such as stress, alcohol use/smoking and mental illness (100). A meta-analysis investigating the link between optimism and health behaviours found

that those who experienced greater optimism engaged in more physical activity, a better diet and less smoking than their less optimistic peers (101), though the effect size was small/modest. As suggested in the meta-analysis, it is likely that there is a bi-directional relationship between optimism and engaging in healthy behaviours, especially physical activity (102) which is also likely present for PTG (103). Sleep is another aspect of health that likely has a bidirectional relationship with psychological thriving. Pre-sleep cognitions, either positive (e.g. gratitude) or negative (e.g. anxiety) have been shown to be associated with quality of sleep (104, 105). A pattern of positive pre-sleep cognitions increasing quality of sleep, quality of sleep increasing mood, and then positive mood increasing the likelihood of positive pre-sleep cognitions, is likely to exist (106) (Chapter 7 figure 4). Finally, in terms of stress, CVD patients who underwent a recent coronary artery bypass graft surgery and were randomised to a positive psychological intervention have been shown to have significantly lower cortisol awakening responses and lower HsCRP compared to control participants ($p<.05$) (107). Similarly, high positive affect, defined as frequency that one experiences positive emotions, has been shown to be associated with lower levels of cortisol 30 minutes post-awakening in a study of US siblings (108). Further research is required to establish whether there is a distinction between PTG and other constructs of psychological thriving, especially with regard to their effects on physiological health and whether this is fully/partially mediated by lifestyle factors (e.g. physical activity, diet).

CHAPTER 7 FIGURE 4: PRE-SLEEP COGNITIONS, SLEEP QUALITY AND MENTAL HEALTH



Retrospective perception of PTG: Perceived growth and actual growth

Measuring PTG is increasingly understood to be a difficult process. Research has indicated that prospective and retrospective studies assessing PTG are measuring two different constructs; actual growth (measured from prospective studies of positive psychological functioning) and perceived growth (measured from retrospective studies). Actual growth is less prevalent compared to perceived growth (109) and perceived growth may not reflect actual growth (110). As time since the trauma increases, which has been found to be associated with increased reporting of perceived growth, a person is more likely to misremember their prior psychological state and may be influenced by social desirability or cultural identity to perceive themselves as 'better' or 'wiser' (111). The use of the DPTGI, as used in this thesis, or the PTGI are measures of perceived growth. Despite the limitations of measuring retrospective perceived growth, it is also true that perceived growth was associated with mostly positive cardiovascular health indicators in this thesis (chapter six). Perception of social support for example, is regularly evidenced as a protective factor against mental illness (32) and CVD (112), but actual social support may differ from perceived social support (113). This emphasises that perhaps perception of social support is more important than actual social support, and as such, even the perception of growth may have power to elicit a positive physiological response. It is important to consider though that retrospective PTG may even just be a reflection of other positive psychological constructs (e.g. optimism), as discussed above. Future research would benefit from at least simply understanding and presenting retrospectively measured PTG as what it is, perceived growth. Additionally, prospective studies of PTG are needed to understand whether actual growth has beneficial properties similar to, or in excess/deficit of, that observed for perceived growth.

Clinical implications

As discussed earlier in this chapter, early intervention is a possible route for mitigating the increased cardiovascular risk observed in those with PTSD. These early intervention strategies tend to focus on factors such as diet and physical exercise, and there is a recommendation for them to also include mental health components (89). Adding a positive psychology component such as optimism training to interventions has already been shown to have a positive effect on populations with increased cardiovascular risk (107, 114), though no known research has investigated positive psychology elements in early intervention strategies (115). It is also of note that pharmaceutical interventions almost exclusively focus on the reduction of mental illness symptoms, not the promotion of symptoms relating to

psychological thriving (115). Shifting focus so both positive psychology/psychological thriving and mental illness are investigated in the scientific community would be beneficial to our understanding of mental health and wellness.

Recommendations for future research

As discussed in chapter six (pg. 282-287) and above, future research would benefit from understanding the mediating effects of physical health, diet and sleep in the relationship between PTG and cardiovascular health; the reasons why spirituality is associated with some aspects of poorer cardiometabolic functioning; the reasons why the PTG factor new possibilities has associations with both positive and negative cardiometabolic effects and haemodynamic functioning; the broader overlap between PTG and other constructs of psychological thriving and the integration of positive psychology components into early intervention strategies aiming to reduce the risk of or delay the development of CVD. Investigation into psychological thriving alongside mental health in mainstream science would have a strong positive impact on our understanding of mental health.

Conclusions

UK Armed Forces personnel who sustained an amputation injury whilst on deployment to Afghanistan are no more likely to report mental illness and more likely to report a large degree of PTG compared to a matched uninjured group. Those who sustained a non-amputation injury are more likely to report mental illness and no more likely to report a large degree of PTG compared to the same matched uninjured group.

Additionally, a wider variety of PTSD symptoms are associated with cardiometabolic effects and haemodynamic functioning than previously hypothesised. Avoidance behaviours, emotional numbing, intrusive thoughts and hyperarousal symptoms all appear to have unique associations with cardiovascular functioning.

Finally, this thesis presents some of the most detailed investigations into PTG and cardiovascular functioning to date. Factors of PTG including appreciation of life, new possibilities, personal strength, relating to others and spiritual change are associated with mostly positive cardiovascular health, however some negative associations also exist.

These findings emphasise the importance of considering mental health alongside physical health. The discussion on mental health should not be limited to mental illness, but also focus on facilitating psychological thriving. By doing so, we maximise the potential of a person's well-being and quality of life, which may be especially important for the long-term recovery

of UK military personnel who have sustained physical injuries. Policy and clinical intervention should strive to facilitate a combination of both physical and psychological thriving.

Chapter 7 References

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Chapter 1 Supplementary Materials 1: Search Terms

Search terms	
	Search terms
1. HEALTH PROBLEMS	**hyperlipi***
	hypertension
	cardiovascular
	heart rate variability
	HRV
	cholesterol
	triglyceride
	Low-Density lipoprotein
	High-Density lipoprotein
	HDL
	LDL
	high sensitivity c-reactive protein
	hs crp
	hscrp
	blood pressure
	coronary
	heart disease
	blood disease
	inflammation
	smoking
	diabetes
	obes*

	interleukin **interferon** **tumor necrosis factor** **body mass index** **tobacco** **myocardial infarction**
2. MILITARY SEARCH TERMS	**vetera*** **ex-serving** **armed forces** **military** **soldier** **officer** **combat** **ex-military**
3. IRAQ/AFGHANISTAN DEPLOYED	**Iraq** **Afghanistan** **Herrick** **telic** **operation enduring freedom** **operation Iraqi freedom** **operation new dawn**
4. PTSD	**PTSD** **PTSS**

	post traumatic stress
5. LIMITS	**2001-Current** **human** **English language** **Full text**

(((PTSD) OR PTSS) OR post traumatic stress) AND ((((((((((((((((((((((((((hyperlipi*) OR hypertension) OR cardiovascular) OR cholesterol) OR triglyceride) OR hs crp) OR hscrp) OR blood pressure) OR coronary) OR heart disease) OR blood disease) OR high sensitivity c-reactive protein) OR heart rate variability) OR HRV) OR dyslipi*) OR Low-Density lipoprotein) OR High-Density lipoprotein) OR HDL) OR LDL) OR inflammation) OR smoking) OR diabetes) OR obes*) OR interleukin) OR interferon) OR tumor necrosis factor) OR body mass index) OR tobacco) OR myocardial infarction)) AND (((((((vetera*) OR ex-serving) OR armed forces) OR military) OR solider) OR officer) OR combat) OR ex-military) AND (((((((iraq) OR afghanistan) OR herrick) OR telic) OR operation enduring freedom) OR operation iraqi freedom) OR operation new dawn

Chapter 1 Supplementary Materials 2: Quality Assessment

Observational/Cross sectional	Agorastos et al., 2013			Bersani et al., 2016			Burg et al., 2017			Buta et al., 2018		
	Fair			Fair			Good			Good		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?	x				x		x			x		
2. Was the study population clearly specified and defined?	x			x			x			x		
3. Was the participation rate of eligible persons at least 50%?			NA			NA			NA			NA
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x			x			X			x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x			x			X			x	

Observational/Cross sectional	Agorastos et al., 2013			Bersani et al., 2016			Burg et al., 2017			Buta et al., 2018		
	Fair			Fair			Good			Good		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			NR			NR			NR	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			CD			CD	X			x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x			x			X			x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x			x			X			x		
10. Was the exposure(s) assessed more than once over time?	x				x		X				x	
11. Were the outcome measures (dependent variables) clearly defined, valid,	x			x			x			x		

Observational/Cross sectional	Agorastos et al., 2013			Bersani et al., 2016			Burg et al., 2017			Buta et al., 2018		
	Fair			Fair			Good			Good		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
reliable, and implemented consistently across all study participants?												
12. Were the outcome assessors blinded to the exposure status of participants?			**NR**			**NR**			**CD**			**CD**
13. Was loss to follow-up after baseline 20% or less?			**NA**			**NA**			**NR**			**NR**
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	**x**			**x**			**x**			**x**		

Observational/Cross sectional	Caska et al., 2014			Frayne et al., 2011			Japuntich et al., 2016		
	Fair			Good			Poor		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	X			X			x		
2. Was the study population clearly specified and defined?	X			X			x		
3. Was the participation rate of eligible persons at least 50%?			NA			NA		x	
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?		x		X			x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x			X			x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x					NR		x	

Observational/Cross sectional	Caska et al., 2014			Frayne et al., 2011			Japuntich et al., 2016		
	Fair			Good			Poor		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			**CD**			**CD**			**NA**
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	**x**			**x**			**x**		
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	**x**			**X**			**x**		
10. Was the exposure(s) assessed more than once over time?		**x**		**X**				**x**	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	**x**			**X**			**x**		
12. Were the outcome assessors blinded to the exposure status of participants?			**NR**			**CD**			**NR**

Observational/Cross sectional	Caska et al., 2014			Frayne et al., 2011			Japuntich et al., 2016		
	Fair			Good			Poor		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
13. Was loss to follow-up after baseline 20% or less?			NA			NA			NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x		x			x		

Observational/Cross sectional	Kirby et al., 2008			Lerman et al., 2016			Lindqvist et al., 2014			Lindqvist et al., 2017		
	Poor			Fair			Good			Good		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x			x			x			x		
2. Was the study population clearly specified and defined?		x		x			x			x		
3. Was the participation rate of eligible persons at least 50%?			NA			NA			NA			NA
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x			x			x			x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x			x			x			x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?		x				NR			NR			NR
7. Was the timeframe sufficient so that one could reasonably expect to see an			CD			CD			CD			CD

Observational/Cross sectional	Kirby et al., 2008			Lerman et al., 2016			Lindqvist et al., 2014			Lindqvist et al., 2017		
	Poor			Fair			Good			Good		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
association between exposure and outcome if it existed?												
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	x				x			x			x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x			x			x			x		
10. Was the exposure(s) assessed more than once over time?		x			x			x			x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x			x			x			x		
12. Were the outcome assessors blinded to the exposure status of participants?			NR			NR			NR			NR
13. Was loss to follow-up after baseline 20% or less?			NA			NA			NA			NA

Observational/Cross sectional	Kirby et al., 2008			Lerman et al., 2016			Lindqvist et al., 2014			Lindqvist et al., 2017		
	Poor			Fair			Good			Good		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x				x		x			x		

Observational/Cross sectional	Maguen et al., 2013			Nazarian et al., 2012			Paulus et al., 2013		
	Fair			Fair			Poor		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x			x			x		
2. Was the study population clearly specified and defined?	x			x			x		
3. Was the participation rate of eligible persons at least 50%?			NR			NA			NA
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x			x			x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x			x			x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?		x			x			x	
7. Was the timeframe sufficient so that one could reasonably expect to see an	x			x					CD

Observational/Cross sectional	Maguen et al., 2013			Nazarian et al., 2012			Paulus et al., 2013		
	Fair			Fair			Poor		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
association between exposure and outcome if it existed?									
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x			x			x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x			x			x		
10. Was the exposure(s) assessed more than once over time?		x		x				x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x			x				x	
12. Were the outcome assessors blinded to the exposure status of participants?			NR			NR			NR
13. Was loss to follow-up after baseline 20% or less?			NR			NR			NR

Observational/Cross sectional	Maguen et al., 2013			Nazarian et al., 2012			Paulus et al., 2013		
	Fair			Fair			Poor		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	**x**			**x**			**x**		

Observational/Cross sectional	Ray et al., 2017			Tan et al., 2009			Cohen et al., 2009		
	Fair			Poor			Fair		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x			x			x		
2. Was the study population clearly specified and defined?		x			x		x		
3. Was the participation rate of eligible persons at least 50%?			NA			NA			NA
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x			x			X		
5. Was a sample size justification, power description, or variance and effect estimates provided?	x				x		X		
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			NR			NR			NR
7. Was the timeframe sufficient so that one could reasonably expect to see an			CD			CD	X		

Observational/Cross sectional	Ray et al., 2017			Tan et al., 2009			Cohen et al., 2009		
	Fair			Poor			Fair		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
association between exposure and outcome if it existed?									
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	x				x			X	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x				x		X		
10. Was the exposure(s) assessed more than once over time?		x			x				NR
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x			x			X		
12. Were the outcome assessors blinded to the exposure status of participants?			NR			NR			CD
13. Was loss to follow-up after baseline 20% or less?			NR			NA			NA

Observational/Cross sectional	**Ray et al., 2017**			**Tan et al., 2009**			**Cohen et al., 2009**		
	Fair			**Poor**			**Fair**		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	**x**				**x**		**x**		

Case Control	Blessing et al., 2017		
	Fair		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated and appropriate?	x		
2. Was the study population clearly specified and defined?	x		
3. Did the authors include a sample size justification?		x	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	x		
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	x		
6. Were the cases clearly defined and differentiated from controls?	x		
7. If less than 100 percent of eligible cases and/or controls were			NA

Case Control	Blessing et al., 2017		
	Fair		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
selected for the study, were the cases and/or controls randomly selected from those eligible?			
8. Was there use of concurrent controls?		x	
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?		x	
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	x		
11. Were the assessors of exposure/risk blinded to the case or control status of participants?		NR	

Case Control	Blessing et al., 2017		
	Fair		
Criteria	Yes	No	Other (CD, NR, NA)*
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	x		

Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group	Ramaswamy et al., 2015		
	Poor		
Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	x		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			NR
4. Were all eligible participants that met the prespecified entry criteria enrolled?	x		
5. Was the sample size sufficiently large to provide confidence in the findings?		x	
6. Was the test/service/intervention clearly described and delivered		x	

Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group	Ramaswamy et al., 2015		
	Poor		
Criteria	Yes	No	Other (CD, NR, NA)*
consistently across the study population?			
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	x		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?			NR
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	x		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	x		
11. Were outcome measures of interest taken multiple times before the		x	

Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group	Ramaswamy et al., 2015		
	Poor		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?			
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			**NA**

Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group	Ginsberg et al.,		
	Poor		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?		x	
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?			NA
3. Was the treatment allocation concealed (so that assignments could not be predicted)?			NA
4. Were study participants and providers blinded to treatment group assignment?		x	
5. Were the people assessing the outcomes blinded to the participants' group assignments?			NR
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	x		
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	x		
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	x		
9. Was there high adherence to the intervention protocols for each treatment group?			NR
10. Were other interventions avoided or similar in the groups (e.g.,			NR

Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group	**Ginsberg et al.,**		
	Poor		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
similar background treatments)?			
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	**x**		
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?		**x**	
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	**x**		
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?			**NA**

Chapter 1 Supplementary Materials 3: methodological data

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
Agorastos, et al., 2013	• **History of any physical or mental comorbidities** • **History of alcohol or other substance abuse** • **BMI diverging from norms** • **Pathological chest x-ray or ECG.**	**NR**	**CAPS (DSM-IV-TR)**	**HRV (ECG)** **HR (LF/HF ratio) (ECG)** **HR (root mean square of subsequent differences/standard deviation of the NN intervals) (ECG)** **BMI (NR)**	**Depression**	**NR**
Bersani et al., 2016	• **history of alcohol dependence within the past 8 months** • **history of drug abuse or dependence within the past year**	**NR**	**SCID; CAPS (DSM-IV)**	**Clinical Hypertension (NR)** **Inflammatory conditions (NR)** **Diabetes Mellitus (NR)**	**DSM-IV Axis 1 disorders**	**Mean 77.33 months (± 25.17) since trauma (Discovery sample)**

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
	• **lifetime history of any psychiatric disorder with psychotic features, bipolar disorder or obsessive-compulsive disorder** • **Those who were currently exposed to recurrent trauma or have been exposed to a traumatic event within the past 3 months** • **Subjects with prominent suicidal or homicidal ideation** • **neurologic disorder or systemic illness affecting central nervous system**					**Mean 51.42 months ± 24.96) since trauma**

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
	function • **history of hepatitis** • **history of anaemia, recent blood donation in the past 2 months** • **subjects on medication who were not stable for 2+ months on psychiatric medication, anticonvulsants, antihypertensive medication or sympathomimetic medication** • **subjects who were classified with a moderate of severe traumatic brain injury**					

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
	on the Ohio State University TBI identification Method short form **• subjects who experienced loss of consciousness for>10 minutes**					
Blessing et al., 2017	**• History of alcohol dependence within the past 8 months** **• history of drug abuse or dependence within the past year** **• Lifetime history of any psychiatric disorder with psychotic features,**	**NR**	**SCID; CAPS (NR)**	**SBP (NR)** **DBP (NR)** **HR (NR)** **Cardiovascular diseases (acute coronary syndrome; stroke; peripheral vascular disease) (self-report)** **HDL (NR)**	**Major Depressive Disorder (SCID)**	**>3 months**

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
	bipolar disorder or obsessive-compulsive disorder **• Exposure to trauma within the past 3 months** **• Suicidal/homicidal ideation** **• neurological disorder or systemic illness affecting CNS** **• Anaemia or blood donation in past 2 months** **• Changes to psychiatric, anticonvulsants, antihypertensive or sympathomimetic medication in the last 2**			**LDL (NR)** **Triglycerides (NR)** **Hypertensive medication (NR)** **BMI (NR)** **Smoking (NR)**		

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
	months • moderate or severe TBI loss of consciousness >10 minutes					
Burg et al., 2017	• Implausible BP values • Hypertension diagnosis, received prescription for antihypertensive or had their first BP reading in hypertensive range before and on day of first BP measurement • Missing sex, ethnicity or baseline BMI data	September 2001-January 2010	Diagnosis (ICD-9: 309.81)	Hypertension (ICD-9-C 401; prescription of anti-hypertensive medication; BP recorded in the hypertensive range) DBP (NR) SBP (NR)	Major Depression; Substance Use Disorder	1 month-8 years
Buta et	• no or only 1 BMI measurement available	October 2001-	ICD-9-	BMI	Major Depression ;Substance Use	NR

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
al., 2018	• unknown race/ethnicity • implausible BMI measurements (<11, >70)	January 2009	CM	BMI (overweight) BMI (obsese)	Disorder	
Caska et al., 2014	• History of Coronary Heart Disease • Taking medication that would affect cardiovascular reactivity (e.g. beta blockers) • Active mania, psychosis, suicidality, homicidality, or alcohol/drug dependence within last 3 months. • Controls only: Axis 1 disorders	NR	CAPS (DSM-IV-TR)	SBP (BP monitor; upper non-dominant arm) DBP (BP monitor; upper non-dominant arm) HR (ECG)	Depression Anxiety	NR
Cohen et	None	October	Diagnosis	Tobacco use (ICD-9)	Depression; Anxiety	NR

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
al., 2009		2001-September 2008	(ICD-9)	Hypertension (ICD-9) Hyperlipidaemia (ICD-9) Obesity (ICD-9) Diabetes Mellitus (ICD-9)	disorder; Adjustment disorder; Alcohol Use Disorder; Substance Use Disorder; Other Psychiatric Diagnoses	
Frayne et al., 2011	None	April 2006-March 2007	Diagnosis (ICD-9: 309.81)	Acute Myocardial infraction (ICD-9) Aortic, peripheral and visceral artery aneurysms (ICD-9) Aortic, peripheral arterial embolism or thrombosis (ICD-9) Cardiac arrest, ventricular fibrillation (ICD-9) Cardiac dysrhythmias (ICD-9) Circulatory diseases (ICD-9) Conduction disorders (ICD-9) Congestive heart failure; non-hypertensive (ICD-9) Coronary Atherosclerosis, other heart disease (ICD-9) Heart Valve Disorders (ICD-9)	stress-related disorders (ICD-9); other (non-PTSD) conditions (ICD-9)	>1 year

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
				Hemorrhoids (ICD-9) **Hyperlipidaemia (ICD-9)** **Hypertension (ICD-9)** **Hypertension with complications, seco** **Hypotension and other miscellaneous** **Other and ill-defined heart disease (IC** **Other diseases of veins, lymphatics (IC**		
Ginsberg et al., 2010	• **mTBI** • **Any neurological disorder** • **history of PTSD, depression, alcohol or substance abuse prior to OIF/OEF** • **History of seizure disorder**	**NR**	**CAPS (NR)**	**HRV power (HRV monitor)** **HRV coherence (HRV monitor)** **HRV VLF (HRV monitor)** **HRV LF (HRV monitor)** **HRV HF (HRV monitor)**	**Depression (Zung Depression Scale); Anxiety (Spielberger State-Trait Anxiety Inventory**	**NR**

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
	• acetylcholine esterase inhibitor/neuroleptic medication use • active substance abuse • lifetime history of major depression, bipolar, psychosis, panic and/or obsessive compulsive disorders • cardiovascular disease					
Japuntich et al., 2016	None	June 2009	PCL-M (NR)	Tobacco use (self-report)	none	NR
Kirby et al., 2008			CAPS (NR)	Tobacco use (Fagerstrom Test for Nicotine Dependence)	DSM-IV Axis 1 disorders	NR

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
Linqvist et al., 2014	• **History of alcohol dependence within the past 8 months** • **drug abuse (excluding nicotine) in past year** • **lifetime history of psychiatric disorder with psychotic features, bipolar disorder, obsessive compulsive disorder** • **exposure to trauma within last 3 months** • **suicidal or homicidal ideation** • **neurological disorder or systemic illness affecting CNS**	**NR**	**CAPS (DSM-IV)**	**CRP (Latex-enhanced immunoturbidimetric assay)** **Interferon-Gamma (Latex-enhanced immunoturbidimetric assay)** **Interleukin-1 (Latex-enhanced immunoturbidimetric assay)** **Interkeukin-6 (Latex-enhanced immunoturbidimetric assay)** **Interleukin-10 (Latex-enhanced immunoturbidimetric assay)** **Tumor Necrosis Factor (Latex-enhanced immunoturbidimetric assay)** **Tobacco use (NR)** **BMI (NR)**	**Depression (BDI-II)**	**>3 months**

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
	• Anaemia or blood donation in past 2 months • subjects who were not on stable psychiatric, anticonvulsant, antihypertensive or sympathomimetic medications • moderate or severe TBI • Experience of loss of consciousness for >10 minutes			Waist to hip ratio Pro-inflammatory cytokine score (Latex-enhanced immunoturbidimetric assay)		
Linqvist et al.,	• History of alcohol dependence within the	NR	CAPS (DSM-	High Sensitivity C-Reactive Protein (Latex-enhanced	Depression (BDI-II)	>3 months

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
2017	**past 8 months** **• drug abuse (excluding nicotine) in past year** **• lifetime history of psychiatric disorder with psychotic features, bipolar disorder, obsessive compulsive disorder** **• exposure to trauma within last 3 months** **• suicidal or homicidal ideation** **• neurological disorder or systemic illness affecting CNS** **• Anaemia or blood donation in past 2**		**IV)**	**immunoturbidimetric assay)** **Interferon-Gamma (Latex-enhanced immunoturbidimetric assay)** **Interleukin-10 (Latex-enhanced immunoturbidimetric assay)** **Interleukin-6 (Latex-enhanced immunoturbidimetric assay)** **Tumor Necrosis Factor-Alpha (Latex-enhanced immunoturbidimetric assay)** **Tobacco use (self report/plasma cotinine levels)** **BMI (NR)** **Pro-inflammatory cytokine score (Latex-enhanced immunoturbidimetric assay)**		

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
	months • **subjects who were not on stable psychiatric, anticonvulsant, antihypertensive or sympathomimetic medications** • **moderate or severe TBI** • **Experience of loss of consciousness for >10 minutes**					
Nazarian et al., 2012	**None.**	**April 2006-March 2007**	**Diagnosis (ICD-9)**	**Cardiovascular diseases (ICD-9)** **Hypertension (ICD-9)** **Chest pain (ICD-9)**	**Substance use disorders (ICD-9)**	**NR**

Author	Exclusion criteria	Data collection period	Definition of PTSD	Physical health outcomes measured measurement type)	Other mental health outcomes investigated	PTSD length
				Hemorrhoids (ICD-9)		
Paulus et al., 2013	**None.**	**January 2008-January 2010**	**Diagnosis (NR)**	**DBP (NR)** **SBP (NR)** **HR (NR)**	**Depression (NR); Anxiety (NR); Mood disorders (NR); Substance abuse (NR)**	**NR**
Ray, Pyne & Gevirtz, 2017	• **Daytime benzodiazepine or beta-blockers use** **Anticholinergic and tricyclic antidepressant use**	**NR**	**CAPS (DSM-IV)**	**HRV (ECG)** **SDNN (ECG)** **HF (ECG)** **RMSSD (ECG)**	**Depression**	**NR**
Tan et al., 2009	**None.**	**NR**	**Diagnosis (NR)**	**HRV (ECG)**	**None**	**NR**

Chapter 1 Supplementary Materials 4: Physical health conditions associated with PTSD

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
Cardiovascular outcomes									
Frayne et al., 2011	Acute Myocardial infraction								AOR 1.21 (95%CI 0.55, 2.65)
Frayne et al., 2011	Aortic, peripheral and visceral artery aneurysms								AOR 1.57 (95%CI 0.78, 3.17)
Frayne et al., 2011	Aortic, peripheral arterial embolism or thrombosis						AOR 8.17 (95%CI 1.80, 37.05)		
Frayne et al., 2011	Cardiac arrest, ventricular fibrillation								AOR 3.16 (95%CI 0.78, 12.73)
Frayne et al., 2011	Cardiac dysrhythmias						AOR 1.36 (95%CI 1.21, 1.52)		
Frayne et al., 2011	Circulatory diseases	30.10%	27.90%				AOR 1.29 (95%CI 1.25-1.34)		
Nazarian et al., 2012	Circulatory diseases	22.80%	22.40%				Circulatory disease as function of		

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
							PTSD AOR 1.10 (95%CI 1.03-1.16)		
Nazarian et al., 2012	Circulatory diseases (chest pain)	6.40%	7.00%						
Frayne et al., 2011	Conduction disorders								AOR 1.17 (95%CI 0.83, 1.65)
Frayne et al., 2011	Congestive heart failure; non-hypertensive								AOR 1.18 (95%CI 0.75, 1.86)
Frayne et al., 2011	Coronary Atherosclerosis, other heart disease						AOR 1.35 (95%CI 1.16, 1.57)		
Cohen et al., 2009	Dyslipidemia	21.00%	10.90%				model 1 OR 2.70 (95%CI 2.63-2.78)		
Cohen et al., 2009	Dyslipidemia						model 2 OR 1.45 (95%CI 1.39-1.50)		
Frayne et al., 2011	Heart Valve Disorders								AOR 0.94 (95%CI 0.79, 1.11)
Frayne et al., 2011	Hematologic diseases	2.20%	2.2						1.05 (95%CI 0.94, 1.17)

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
Frayne et al., 2011	**Hemorrhoids**						**AOR 1.26 (95%CI 1.15, 1.37)**		
Nazarian et al., 2012	**Hemorrhoids**	**4.00%**	**3.90%**						
Frayne et al., 2011	**Hyperlipidaemia**	**14.40%**	**11.90%**				**AOR 1.15 (95%CI 1.10-1.19)**		
Cohen et al., 2009	**Hypertension**	**16.40%**	**8.10%**				**model 1 OR 2.88 (95%CI 2.79-2.97)**		
Cohen et al., 2009	**Hypertension**						**model 2 OR 1.56 (95%CI 1.50-1.63)**		
Frayne et al., 2011	**Hypertension**	**20.20%**	**19.50%**				**AOR 1.24 (95%CI 1.19-1.30)**		
Nazarian et al., 2012	**Hypertension**	**22.70%**	**23.20%**						
Frayne et al., 2011	**Hypertension**						**AOR 1.24 (95%CI 1.19, 1.30)**		
Bersani et al., 2016	**Hypertension**	**7**	**3**			**Mann Whitey U-test x2=.10 *p*>.05**			

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
Bersani et al., 2016	**Hypertension**	**3**	**6**			**Mann Whitey U-test x2=.25 *p*>.05**			
Paulus et al., 2013	**Hypertension (diagnosed and un-diagnosed)**	**34.09%**	**16.33%**						
Burg et al. 2017	**Hypertension event**						**Non-treatment seeking AHR 1.37 (95% CI 1.33-1.40) (*p*<.01)**		
Burg et al. 2017	**Hypertension event**						**Treatment seeking AHR 1.13 (95%CI 1.10-1.16) (*p*<.01)**		
Frayne et al., 2011	**Hypertension with complications, secondary hypertension**								**AOR 0.83 (95%CI 0.58, 1.19)**
Frayne et al., 2011	**Hypotension and other miscellaneous circulatory conditions**						**AOR 1.28 (1.09, 1.49)**		
Frayne et al., 2011	**Other and ill-defined heart disease**								**AOR 1.23 (95%CI 0.95, 1.59)**
Frayne et al.,	**Other diseases of veins, lymphatics**								**AOR 1.05**

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
2011									**(95%CI 0.86, 1.28)**
Frayne et al., 2011	**Peri-;Endo-;myocarditis; cardiomyopathy (except TB, STD)**								**AOR 1.20 (95%CI 0.84, 1.72)**
Frayne et al., 2011	**Peripheral and visceral Atherosclerosis**						**AOR 8.17 (95%CI 1.80, 37.05)**		
Frayne et al., 2011	**Phlebitis; thrombophlebitis and thromboembolism**								**AOR 1.20 (95%CI 0.90, 1.60)**
Frayne et al., 2011	**Pulmonary Heart Disease**						**AOR 1.63 (95%CI 1.04, 2.56)**		
Diabetes									
Bersani et al., 2016	**Diabetes**	**3**	**0**			**Mann Whitney U-test x2=.13 *p*>.05**			
Bersani et al., 2016	**Diabetes**	**1**	**1**			**Mann Whitney U-test x2=.83 *p*>.05**			
Frayne et al., 2011	**Diabetes**	**4.10%**	**4.60%**				**AOR 1.08 (95%CI 1.00,**		

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
							1.17)		
Nazarian et al., 2012	Diabetes	3.80%	4.50%				Endocrine/metabolic disease as function of PTSD AOR 1.07 (95%CI 1.01, 1.13)		
Cohen et al., 2009	Diabetes	2.00%	1.10%				AOR 2.57 (95%CI 2.37, 2.78)		
Cohen et al., 2009	Diabetes						Model 2 AOR 1.07 (0.969, 1.18)		
Heart function									
Blessing et al., 2017	Diastolic Blood Pressure (NR)	72.58 ± 8.20	70.50 ± 8.16			ANOVA d=.25 (*p*=.11)			ANCOVA d=.25 (*p*=.08)
Paulus et al., 2013	Diastolic Blood Pressure (NR)	87.60 ± 6.30	No PTSD 78.40 ± 7.20	Two sample t-test df=184 d=1.36 (*p*<.001)					
Paulus et al., 2013	Diastolic Blood Pressure (NR)		No trauma 77.10 ± 6.80	ANOVA PTSD+, PTSD- and no trauma F=48.48					

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
				(*p*<.05)					
Paulus et al., 2013	Diastolic Blood Pressure (NR)						PTSD+ and PTSD- ANCOVA (sig)		
Caska et al., 2014	Diastolic Blood Pressure (sitting)	76.60 ± 8.50	79.00 ± 8.50						
Agorastos et al, 2013	Heart Rate (24 hour)	64.10 ± 4.20	56.80 ± 6.80	t-test t=-2.45 df=13 (*p*=.03)			ANCOVA f=8.49 (*p*=.02)		
Agorastos et al, 2013	Heart Rate (day time)	64.50 ± 3.80	59.10 ± 6.20			t-test t=-1.97 df=13 (*p*=.07)			ANCOVA f=.53 (*p*=.48)
Blessing et al., 2017	Heart Rate (daytime)	72.36 ± 10.38	64.25 ± 11.01	ANOVA d=.76 (*p*<.01)			ANCOVA d=.71 (*p*<.01)		
Paulus et al., 2013	Heart Rate (likely daytime)	78.90 ± 9.80	73.10 ± 8.00	Two sample t-test df=184 d=0.65 (*p*<.001)					
Caska et al., 2014	Heart Rate (likely daytime) (sitting)	75.60 ± 12.10	67.80 ± 10.50						
Agorastos et al, 2013	Heart Rate (night time)	61.30 ± 6.50	51.80 ± 7.50	t-test t=-2.61 df=13 (*p*=.02)			ANCOVA f=6.49 (*p*=.03)		
Ginsberg, Berry & Powell, 2010	Heart Rate Variability Coherence	0.20	1.20						

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
Ginsberg, Berry & Powell, 2010	**Heart Rate Variability High Frequency (ms2/Hz)**	**150.70**	**184.20**						
Ray et al., 2017	**Heart Rate Variability ln(High Frequency)**	**PTSD 5.25 ± 1.26**	**-4.76 ± 1.78**			**Pearson correlation CAPS-ln(HF) -.09 (*p*>.05)**			
Ray et al., 2017	**Heart Rate Variability ln(High Frequency)**	**PTSD + AUD 5.63 ± 1.16**							
Ginsberg, Berry & Powell, 2010	**Heart Rate Variability Low Frequency (ms2/Hz)**	**253.10**	**527.70**						
Agorastos et al, 2013	**Heart Rate Variability Low Frequency/High Frequency (24 hour)**	**2.25 ± 1.34**	**1.05± 0.52**	**t-test t=-2.34 df=13 (*p*=.04)**					**ANCOVA f= 2.19 (*p*=.17)**
Agorastos et al, 2013	**Heart Rate Variability Low Frequency/High Frequency (day)**	**2.72 ± 1.93**	**1.20 ± 0.53**			**t-test t=-2.02 df=6.79 (*p*=.08)**			**ANCOVA f= 3.05 (*p*=.11)**
Agorastos et al, 2013	**Heart Rate Variability Low Frequency/High Frequency(night)**	**1.73 ± 0.97**	**0.76 ± 0.35**	**t-test t=-2.52 df=7.31 (*p*=.04)**					**ANCOVA f= 8.63 (*p*=.01)**
Ginsberg, Berry & Powell, 2010	**Heart Rate Variability Power (ms2/Hz)**	**813.00**	**1142.00**						
Ray et al.,	**Heart Rate Variability Root Mean Square**	**PTSD**	**42.00 ±**			**Pearson**			

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
2017	**of the Successive Differences**	**23.82 ± 14.11**	**15.00**			**correlation CAPS-RMSSD .05 (*p*>.05)**			
Ray et al., 2017	**Heart Rate Variability Root Mean Square of the Successive Differences**	**PTSD + AUD 29.47 ± 15.86**							
Agorastos et al, 2013	**Heart Rate Variability Root Mean Square of the Successive Differences (24 hour)**	**65.10 ± 32.90**	**106.90 ± 43.00**			**t-test t=2.08 df=13 (*p*=.06)**			**ANCOVA f=1.59 (*p*=.24)**
Agorastos et al, 2013	**Heart Rate Variability Root Mean Square of the Successive Differences (day time)**	**63.50 ± 27.20**	**104.00 ± 43.60**		**t-test t=2.12 df=13 (*p*=.05)**				**ANCOVA f=.60 (*p*=.46)**
Agorastos et al, 2013	**Heart Rate Variability Root Mean Square of the Successive Differences (night time)**	**69.90 ± 41.50**	**114.20 ± 51.50**			**t-test t=1.98 df=13 (*p*=.07)**			**ANCOVA f=2.29 (*p*=.17)**
Ray et al., 2017	**Heart Rate Variability: Standard Deviation of the Normal Normal Interval**	**PTSD 29.75 ± 29.75**	**50.00 ± 16.00**			**Pearson's correlation CAPS-SDNN .05 (*p*>.05)**			
Ray et al., 2017	**Heart Rate Variability: Standard Deviation of the Normal Normal Interval**	**PTSD + AUD 35.63 ± 18.86**							
Tan et al., 2009	**Heart Rate Variability: Standard Deviation of the Normal Normal Interval**	**44.96 ± 19.78**	**51.46 ± 34.48**						
Agorastos et al, 2013	**Heart Rate Variability: Standard Deviation of the Normal Normal Interval Interval (24 hour)**	**127.50 ± 30.61**	**155.00 ± 55.40**			**t-test t=1.16 df=13 (*p*=.27)**			**ANCOVA f= .10 (*p*=.76)**

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
Ramaswamy et al., 2015	**HF (ln) at rest**	**6.31 ± 1.16**							
Ramaswamy et al., 2015	**HF (ln) deep breathing**	**7.37 ± 2.57**							
Ray et al., 2017	**High Frequency Heart Rate Variability**	**PTSD 315.89 ± 509.96**	**657 ± 777**						
Ray et al., 2017	**High Frequency Heart Rate Variability**	**PTSD + AUD ± 467.66**							
Ramaswamy et al., 2015	**LF (ln) at rest**	**6.53 ± 1.11**							
Ramaswamy et al., 2015	**LF (ln) deep breathing**	**8.37 ± 2.77**							
Agorastos et al, 2013	**Nonlinear analysis (fast-day)**	**1.15 ± 0.19**	**0.93 ± 0.15**	**t-test t=2.47 df=13 (*p*=.03)**					**ANCOVA f= 3.68 (*p*=.09)**
Agorastos et al, 2013	**Nonlinear analysis (fast-night)**	**1.07 ± 0.22**	**0.87 ± 0.17**			**t-test t=-2.00 df=13 (*p*=.07)**			**ANCOVA f= 4.11 (*p*=.08)**
Agorastos et al, 2013	**Nonlinear analysis (slow-day)**	**0.96 ± 0.10**	**1.00 ± 0.05**			**t-test t=0.82 df=13 (*p*=.43)**			**ANCOVA f= .93 (*p*=.36)**
Agorastos et al, 2013	**Nonlinear analysis (slow-night)**	**1.00 ± 0.09**	**1.08 ± 0.06**			**t-test t=2.04 df=13 (*p*=.06)**			**ANCOVA f= 2.49 (*p*=.15)**
Agorastos et al, 2013	**Normal Normal Interval (24 hour)**	**942.40 ± 59.00**	**1076.70 ± 131.90**		**t-test t=2.48 df=13 (*p*=.03)**			**ANCOVA f=6.45**	

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
								(*p*=.03)	
Agorastos et al, 2013	Normal Normal Intervals that differ by >50ms (24 hour) (%)	32.20% ± 18.80	48.70% ± 18.30			t-test t=1.71 df=13 (*p*=.11)			ANCOVA f= 2.23 (*p*=.16)
Agorastos et al, 2013	Normal Normal Intervals that differ by >50ms (24 hour) (n)	28633.10 ± 17055.0	37713.10 ± 13445.50			t-test t=1.15 df=13 (*p*=.27)			ANCOVA f= 1.08 (*p*=.32)
Ramaswamy et al., 2015	QT	375 ± 43							
Ramaswamy et al., 2015	Qtvi (at rest)	-1.82 ± 0.43							
Ramaswamy et al., 2015	Qtvi (deep breathing)	-1.76 ± 0.31							
Ramaswamy et al., 2015	Inter Beat Interval mean (ms)	941 ± 161							
Blessing et al., 2017	Systolic Blood Pressure (NR)	117.16 ± 10.65	118.83 ± 10.70			ANOVA d=-.16 (*p*=.33)			ANCOVA d=-.15 (*p*=.37)
Paulus et al., 2013	Systolic Blood Pressure (NR)	133.80 ± 8.60	No PTSD 122.30 ± 9.60	Two sample t-test df=184 d=1.27 (*p*<.001)					
Paulus et al., 2013	Systolic Blood Pressure (NR)		No trauma 120.10 ± 8.90	ANOVA PTSD+, PTSD- and no trauma F=50.13					

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
				(p<.05)					
Paulus et al., 2013	Systolic Blood Pressure (NR)						PTSD+ and PTSD- ANCOVA (sig)		
Caska et al., 2014	Systolic Blood Pressure (sitting)	120.00 ± 11.50	122.60 ± 12.40						
Ginsberg, Berry & Powell, 2010	Very Low Frequency Heart Rate Variability(ms2/Hz)	409.60	430.30						
Inflammation									
Blessing et al., 2017	C-Reactive Protein	3.62 ± 5.52	1.48 ± 2.14	ANOVA d=.51 (p<.01)			ANCOVA d=.48 (p<.01)		
Lindqvist et al., 2014	C-Reactive Protein	3.27 ± 5.66	1.66 ± 2.30						ANCOVA f=1.08 (p=.301)
Lindqvist et al., 2017	High Sensitivity C-Reactive Protein	4.10 ± 5.18	1.59 ± 2.58	Student's T-test df=89 t=2.86 (p<.01)			ANCOVA f=6.06 (p<.05)		
Lerman et al., 2016	IL-10	.38 ± .35	0.41 ± .28			NR			
Lerman et al., 2016	IL-1b	0.1 ± .01	0.17 ± .07			NR			
Bersani et al., 2016	Inflammatory conditions	1	3			Mann Whitney U-			

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
						test x2=.31 *p*>.05			
Bersani et al., 2016	Inflammatory conditions	1	1			Mann Whitney U-test x2=.87 *p*>.05			
Lindqvist et al., 2014	Interferon-Gamma	1.41 ± 1.79	0.65 ± 0.38				ANCOVA f=8.13 (*p*=.005)		
Lindqvist et al., 2017	Interferon-Gamma	6.16 ± 7.06	3.60 ± 1.45			Student's T-test t=0.53 (*p*>.10)			ANCOVA f=.03 (*p*>.10)
Lindqvist et al., 2014	Interkeukin-1	0.14 ± 0.17	0.11 ± 0.10						ANCOVA f=2.55 (*p*=.114)
Lindqvist et al., 2014	Interleukin-10	2.15 ± 1.49	1.94 ± 1.47						ANCOVA f=1.98 (*p*=.163)
Lindqvist et al., 2017	Interleukin-10	0.26 ± 0.12	0.28 ± 0.26			Student's T-test t=1.53 (*p*>.10)			ANCOVA f=2.00 (*p*>.10)
Lindqvist et al., 2014	Interleukin-6	1.04 ± 0.85	0.81 ± 0.78						ANCOVA f=2.82 (*p*=.096)
Lindqvist et al., 2017	Interleukin-6	0.60 ± 0.51	0.35 ± 0.19	Student's T-test t=3.10 (*p*<.01)			ANCOVA f=6.86 (*p*<.05)		

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
Blessing et al., 2017	**Interleukin-6**	**1.04 ± 0.85**	**0.80 ± 0.79**	**ANOVA d=.29 *p*=.01**					**ANCOVA d=.25 (*p*>.05)**
Lindqvist et al., 2014	**Pro-inflammatory cytokine score**	**0.89 ± 3.48**	**-0.81 ± 2.45**				**ANCOVA f=10.02 (df1,90) *p*=.002**		
Lindqvist et al., 2017	**Pro-inflammatory cytokine score**	**1.03 ± 2.99**	**-0.97 ± 2.31**	**Independent t-test t=2.91 p=<.01**			**ANCOVA f=5.47 *p*<.05**		
Lindqvist et al., 2014	**Tumor Necrosis Factor-Alpha**	**4.27 ± 4.00**	**3.07 ± 0.70**				**ANCOVA f=8.32 (*p*=005)**		
Lindqvist et al., 2017	**Tumor Necrosis Factor-Alpha**	**3.40 ± .359**	**3.30 ± 5.80**			**Student's T-test t=1.80 (*p*<.10)**			**ANCOVA f=2.24 (*p*>.10)**
Blessing et al., 2017	**Tumor Necrosis Factor-Alpha**	**4.23 ± 3.98**	**3.06 ± 0.70**	**ANOVA d=.41 (*p*=.03)**			**ANCOVA d=.37 (*p*<.05)**		
Lipids									
Blessing et al., 2017	**Cholesterol**	**179.73 ± 36.25**	**171.14 ± 27.72**			**ANOVA d=.27 (*p*=.09)**			**ANCOVA d=.24 (*p*=.13)**
Blessing et al., 2017	**High-Density Lipoprotein**	**47.80 ± 12.54**	**50.09 (13.11**			**ANOVA d=-0.18 (*p*=.26)**			**ANCOVA d=-.15 (*p*=.35)**
Nazarian et al., 2012	**lipid metabolism**	**27.60%**	**24.90%**				**Endocrine/metabolic disease as function of PTSD AOR**		

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
							1.07 (95%CI 1.01, 1.13)		
Blessing et al., 2017	Triglycerides	121.49 ± 68.10	100.59 ± 74.64	ANOVA d=.29 (*p*=.02)			ANCOVA d=.23 (*p*<.05)		
Obesity									
Buta et al., 2018	BMI			Association between PTSD and BMI trajectory Estimate=28.5 (SE .01) p,.001					
Buta et al., 2018	BMI	.10kg/m2 per year	.26kg/m2 per year	Association between PTSD and BMI slope (per year) *p*<.001					
Buta et al., 2018	BMI						Association between PTSD and BMI trajectory estimate=.45 SE=.02 *p*<.001		
Buta et al., 2018	BMI						Association between PTSD and		

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
							BMI slope (per year) *p*<**.001**		
Maguen et al., 2013	**BMI**	**28.6 ± 4.73**	**28.5 ± 4.52**						
Agorastos et al, 2013	**BMI**	**25.70 ± 2.00**	**26.50 ± 2.30**			**T-test (df15) d 0.40** *p*=**.480**			
Blessing et al., 2017	**BMI**	**29.90 ± 5.00**	**28.40 ± 4.80**	**t test** *p*=**.04**					
Lindqvist et al., 2014	**BMI**	**29.90 ± 5.10**	**28.30 ± 4.20**			**-1.71 (df 100)** *p*=**.09**			
Lindqvist et al., 2017	**BMI**	**30.00 ± 5.00**	**28.80 ± 5.80**			**0.85 (df56)** *p*=**.40**			
Maguen et al., 2013	**Obese class 1 (BMI 30-35)**	**43455 (25.9%)**	**67236 (25%)**						
Maguen et al., 2013	**Obese class 2 (35-40)**	**18407 (6.8%)**	**13017 (6.8%)**						
Maguen et al., 2013	**Obese class 3 (40+)**	**3928 (1.7%)**	**2827 (1.5%)**						
Maguen et al., 2013	**Obese losing weight over 3 years**	**3216 (1.2%)**	**3625 (2.2%)**				**Age and Race AOR 1.25 (95%CI 1.19, 1.31)**		
Maguen et	**Obese losing weight over 3 years**						**Full AOR**		

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
al., 2013							**1.15 (95%CI 1.10, 1.21)**		
Maguen et al., 2013	**Obese stable weight over 3 years**	**16493 (6.1%)**	**12268 (6.3%)**				**Stable obese versus stable overweight Age and Race AOR 1.22 (95%CI 1.18, 1.25)**		
Maguen et al., 2013	**Obese stable weight over 3 years**						**Stable obese versus stable overweight full AOR 1.15 (95%CI 1.11, 1.18)**		
Frayne et al., 2011	**Overweight/Obese**	**13.50%**	**11.90%**				**AOR 1.22 (95%CI 1.16, 1.28)**		
Maguen et al., 2013	**Overweight/Obese gaining weight over 3 years**	**3642 (1.4%)**	**5336 (3.2%)**				**Age and Race AOR 1.42 (95%CI 1.37, 1.48)**		
Maguen et al., 2013	**Overweight/Obese gaining weight over 3 years**						**Full AOR 1.20 (95%CI 1.15, 1.25)**		

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
Nazarian et al., 2012	**Overweight/obesity**	**15.20%**	**13.60%**				**Endocrine/metabolic disease as function of PTSD AOR 1.07 (95%CI 1.01, 1.13)**		
Lindqvist et al., 2014	**Waist to hip ratio**	**0.91 (0.08)**	**0.89 (0.12)**			**-1.60 (df 100) *p*=.41**			
Tobacco use									
Kirby et al., 2008	**Current smoker**	**29 (32%)**							
Kirby et al., 2008	**Heavy smokrs (>20 cigarettes/day**	**15 (50%)**							
Kirby et al., 2008	**Lifetime smoker**	**61 (68%)**							
Blessing et al., 2017	**Smoking every day/some days**	**21 (32%)**	**9 (12%)**	**t test *p*=.005**					
Japuntich et al., 2016	**Tobacco**								**PTSD symptoms and changes in tobacco use post-deployment (NR)**
Cohen et al., 2009	**Tobacco use**	**30.80%**	**9.8%**				**model 1 OR 3.63 (95%CI 3.54-3.71)**		

Author	Measure	PTSD+ sample	PTSD- sample	Univariable Analysis			Multivariable analysis		
				Positive association	Negative Association	Non-significant association	Positive association	Negative Association	Non-significant association
Cohen et al., 2009	**Tobacco use**						**model 2 OR 2.61 (95%CI 2.52, 2.71)**		
Lindqvist et al., 2014	**Tobacco use**	**11 (21.57%)**	**3 (5.90%)**	**8.28 (df 2) *p*=.016**					
Lindqvist et al., 2017	**Tobacco use**	**13 (42%)**	**5 (17%)**	**4.68 (DF1) *p*=.031**					
Paulus et al., 2013	**Tobacco use**	**27%**	**33%**						
Ray et al., 2017	**Tobacco use**	**30.00%**							
Ray et al., 2017	**Tobacco use**					**Pearson's correlation CAPS score and Tobacco use .14**			

Chapter 2 Supplementary Materials 1: IMPACTS questionnaire

QUESTIONNAIRE – IMPACTS Study

ADVANCE
WITH KNOWLEDGE AS OUR GUIDE

ARMED
SERVICES
TRAUMA
REHABILITATION
OUTCOME
STUDY

Participant Study Number: A D V / ☐☐☐☐

Date: ____/ ____/ _____ (dd/mm/yyyy)

Bolt-on V1.1 20180522

Participant Study Number: A D V /☐☐☐☐

"All of the information you give us in the questionnaire is stored securely. No-one outside of the research team will be able to identify you from the answers you give in this questionnaire. The only time we might share your personal identifiers (your name, date of birth, NHS number) would be in order to link these to other datasets (for example, with your medical records if you have consented for us to do so). We will NOT pass any of your contact details (address, email address or phone number) to third parties)."

CONTENTS

Section	Questionnaire	Page no.
BO1	Insomnia Severity Index/Pittsburgh Sleep	3
BO2	Multidimensional Scale of Perceived Lifestyle Factors	4
BO3	Growing Up	5
BO4	Post-Traumatic Psychological Growth	6

Participant Study Number: A D V /☐☐☐☐

BO1

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the **past month only**. Please answer all questions.

During the past month, when have you usually gone to bed at night?	USUAL BED TIME:_____am/pm				
During the past month, how long (in minutes) has it usually taken you to fall asleep each night?	NUMBER OF MINUTES:_____				
During the past month, when have you usually gotten up in the morning?	USUAL GETTING UP TIME:_____ am/pm				
During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed)	HOURS OF SLEEP PER NIGHT:_____				
Have you had any of the following problems in the last month?					
Difficulty falling asleep	None ☐	Mild ☐	Moderate ☐	Severe ☐	Very Severe ☐
Difficulty staying asleep	None ☐	Mild ☐	Moderate ☐	Severe ☐	Very Severe ☐
Can you tell us how you rate your sleep?					
How satisfied or dissatisfied are you with your current sleep pattern?	Very satisfied ☐	Satisfied ☐		Dissatisfied ☐	Very Dissatisfied ☐
If you have a sleep problem, does it **INTEFERE** with your daily functioning? (e.g. tiredness, work duties, memory etc.)	Not at all interfering ☐	A little bit ☐	Somewhat ☐	Quite a bit ☐	Extremely ☐

Participant Study Number: A D V/☐☐☐☐

BO2

We are interested in how you feel about the following statements. Read each statement carefully.
Indicate how you feel about each statement.

	Very Strongly Disagree	Strongly Disagree	Mildly Disagree	Neutral	Mildly Agree	Strongly Agree	Very Strongly Agree
There is a special person who is around when I am in need	☐	☐	☐	☐	☐	☐	☐
There is a special person with whom I can share my joys and sorrows	☐	☐	☐	☐	☐	☐	☐
My family really tries to help me	☐	☐	☐	☐	☐	☐	☐
I get the emotional help and support I need from my family	☐	☐	☐	☐	☐	☐	☐
I have a special person who is a real source of comfort to me	☐	☐	☐	☐	☐	☐	☐
My friends really try to help me	☐	☐	☐	☐	☐	☐	☐
I can count on my friends when things go wrong	☐	☐	☐	☐	☐	☐	☐
I can talk about my problems with my family	☐	☐	☐	☐	☐	☐	☐
I have friends with whom I can share my joys and sorrows	☐	☐	☐	☐	☐	☐	☐
There is a special person in my life who cares about my feelings	☐	☐	☐	☐	☐	☐	☐
My family is willing to help me make decisions	☐	☐	☐	☐	☐	☐	☐
I can talk about my problems with my friends	☐	☐	☐	☐	☐	☐	☐

Participant Study Number: A D V/☐☐☐☐

BO3

People come to the military from a variety of different backgrounds. We are interested to see if and how experiences before you joined the Armed Forces affect your health and wellbeing.

Please read the following statements and tick TRUE or FALSE for each.

(Please tick ONE option for each statement)

When I was growing up...	TRUE	FALSE
I came from a close family	☐	☐
I used to get shouted at a lot at home	☐	☐
I often used to play truant from school	☐	☐
I felt valued by my family	☐	☐
I regularly used to see or hear physical fighting or verbal abuse between my parents	☐	☐
In my family there was at least one member I could talk to about things that were important to me	☐	☐
I used to get hit/hurt by a parent or caregiver regularly	☐	☐
One (or more) of my parents had problems with alcohol or drugs	☐	☐
My family used to do things together	☐	☐
I often used to get into physical fights at school	☐	☐
I was suspended/expelled from school (ever)	☐	☐
I did things that should have got me (or did get me) in trouble with the police	☐	☐

Participant Study Number: A D V /

BO4

Some people report that their views and attitudes change **for the better** as a result of deployments.

Below is a list of areas where you may have experienced change. Please read each statement and tell us whether you have changed **for the better** as result of ALL your deployments to Iraq/Afghanistan since 2002.

As a result of my deployment(s) to Iraq or Afghanistan since 2002:	No change for the better	A small change for the better	A medium change for the better	A big change for the better
The things I see as being really important in my life have changed	☐	☐	☐	☐
I appreciate the value of my own life more	☐	☐	☐	☐
I developed new interests	☐	☐	☐	☐
I developed a greater feeling of self-reliance	☐	☐	☐	☐
I developed a better understanding of spiritual matters	☐	☐	☐	☐
I can see more clearly that I can count on people in times of trouble	☐	☐	☐	☐
I set up a new direction for my life	☐	☐	☐	☐
I feel closer to other people	☐	☐	☐	☐
I am more willing to express my emotions	☐	☐	☐	☐
I am more confident that I can handle difficulties	☐	☐	☐	☐
I am able to do better things with my life	☐	☐	☐	☐
I am better able to accept the way things work out	☐	☐	☐	☐
I can better appreciate each day	☐	☐	☐	☐
New opportunities are available which wouldn't have been otherwise	☐	☐	☐	☐
I am more understanding of others	☐	☐	☐	☐
I put more effort into my relationships	☐	☐	☐	☐
I am more likely to try to change things that need changing	☐	☐	☐	☐
I have a stronger religious faith	☐	☐	☐	☐
I discovered that I am stronger than I thought I was	☐	☐	☐	☐
I learned to appreciate other people	☐	☐	☐	☐
I am more able to accept that I need other people	☐	☐	☐	☐

CHAPTER 2 SUPPLEMENTARY MATERIALS 2: POST-TRAUMATIC STRESS DISORDER SYMPTOM CLUSTERS FROM PCL-C

	PCL-C	Symptom cluster
1	(a) Repeated, disturbing memories, thoughts or images of a stressful experience from the past?	Intrusive thoughts
2	(b) Repeated, disturbing dreams of a stressful experience from the past?	Intrusive thoughts
3	(c) Suddenly acting or feeling as if a stressful experience were happening again (as if you were reliving it)?	Intrusive thoughts
4	(d) Feeling very upset when something reminded you of a stressful experience from the past?	Intrusive thoughts
5	(e) Having physical reactions (e.g. heart pounding, trouble breathing, sweating) when something reminded you of a stressful experience from the past?	Intrusive thoughts
6	(f) Avoiding thinking about or talking about a stressful experience from the past or avoiding having feelings related to it?	Avoidance behaviours
7	(g) Avoiding activities or situations because they reminded you of a stressful experience from the past?	Avoidance behaviours
8	(h) Trouble remembering important parts of a stressful experience from the past?	Emotional numbing
9	(i) Loss of interest in activities that you used to enjoy?	Emotional numbing
10	(j) Feeling distant or cut off from other people?	Emotional numbing
11	k) Feeling emotionally numb or being unable to have loving feelings for those close to you?	Emotional numbing
12	(l) Feeling as if your future will somehow be cut short?	Emotional numbing
13	(m) Trouble falling or staying asleep?	Hyperarousal
14	(n) Feeling irritable or having angry outbursts?	Hyperarousal

15	**(o) Having difficulty concentrating?**	**Hyperarousal**
16	**(p) Being 'super alert' or watchful or on guard?**	**Hyperarousal**
17	**(q) Feeling 'jumpy' or easily startled?**	**Hyperarousal**

Chapter 2 Supplementary Materials 3: Deployment-related Post-Traumatic Growth Inventory Factors

	DPTGI item	Factor
1	The things I see as being really important in my life have changed	Appreciation of life
2	I appreciate the value of my own life more	Appreciation of life
3	I developed new interests	New possibilities
4	I developed a greater feeling of self-reliance	Personal Strength
5	I developed a better understanding of spiritual matters	Spiritual change
6	I can see more clearly that I can count of people in times of trouble	Relating to others
7	I set up a new direction for my life	New possibilities
8	I feel closer to other people	Relating to others
9	I am more willing to express my emotions	Relating to others
10	I am more confident that I can handle difficulties	Personal strength
11	I am able to do better things with my life	New possibilities
12	I am better able to accept the way things work out	Personal strength
13	I can better appreciate each day	Appreciation of life
14	New opportunities are available which would have been otherwise	New possibilities
15	I am more understanding of others	Relating to others
16	I put more effort into my relationships	Relating to others
17	I am more likely to try to change things that need changing	New possibilities
18	I have a stronger religious faith	Spiritual change
19	I discovered that I am stronger than I thought I was	Personal strength
20	I learned to appreciate other people	Relating to others

21	**I am more able to accept that I need other people**	**Relating to others**

CHAPTER 3 SUPPLEMENTARY MATERIALS 1: CHOICE OF PRIMARY MEASURE

Patient Health Questionnaire-9 (PHQ9)

Reason for inclusion: the PHQ9 is a well-validated and widely used measure of depression (1). The brief nature of the measure was deemed appropriate so as to reduce questionnaire burden/fatigue throughout the study day. The measure has been translated to many difference languages, however no translations were used as part of this study. The measure has been used in other studies of UK military mental health (2, 3).

Psychometric properties: The acceptability of diagnostic properties of the PHQ9 have been well researched and a cut-off of 10 has been found to be an acceptable cut off point for diagnosing depression (4, 5).

Permission/Payment required: No

Translations available: Yes

Questionnaire length: 9 items

Generalised Anxiety Disorder-7 (GAD7)

Reason for inclusion: the GAD7 is a well-validated and widely used measure of anxiety (6). The brief nature of the measure was deemed appropriate so as to reduce questionnaire burden/fatigue throughout the study day. The measure has been translated to many difference languages, however no translations were used as part of this study. The measure has been used in other studies of UK military mental health (2, 3).

Psychometric properties: The acceptability of diagnostic properties of the GAD7 have been well researched and a cut-off of 10 has been found to be an acceptable cut off point for diagnosing anxiety (5).

Permission/Payment required: No

Translations available: Yes

Questionnaire length: 7 items

Post-Traumatic Check List-Civilian

Reason for inclusion: The PCL-C is a well validated and widely used measure of PTSD (7), according to the DSM-IV definition of PTSD. The measure has been translated to many different languages, however no translations were used as part of this study. The measure has been used in other studies of UK military mental health (2, 3, 8) and is often used in research of US military.

Psychometric properties: The acceptability of diagnostic properties of the PCL-C have been well researched and a cut-off point of 50 has been found to be an acceptable cut off point for diagnosing PTSD (7, 9).

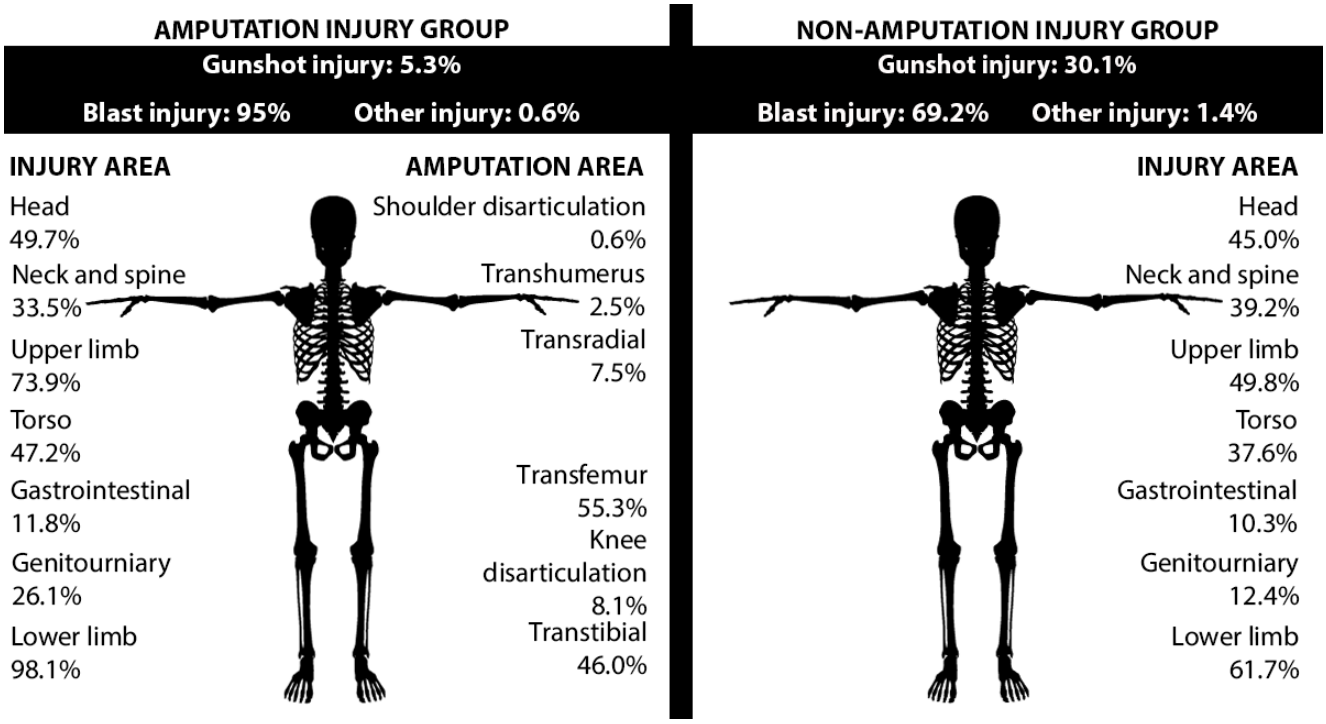
Permission/Payment required: No

Translations available: Yes

Questionnaire length: 17 items

1. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine. 2001;16(9):606-13.
2. Iversen AC, van Staden L, Hughes JH, Browne T, Hull L, Hall J, et al. The prevalence of common mental disorders and PTSD in the UK military: using data from a clinical interview-based study. BMC psychiatry. 2009;9(1):1-12.
3. Stevelink SA, Jones N, Jones M, Dyball D, Khera CK, Pernet D, et al. Do serving and ex-serving personnel of the UK armed forces seek help for perceived stress, emotional or mental health problems? European journal of psychotraumatology. 2019;10(1):1556552.
4. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. Cmaj. 2012;184(3):E191-E6.
5. Kroenke K, Spitzer RL, Williams JB, Löwe B. The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. General hospital psychiatry. 2010;32(4):345-59.
6. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine. 2006;166(10):1092-7.
7. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD Checklist (PCL). Behaviour research and therapy. 1996;34(8):669-73.
8. Stevelink SA, Jones M, Hull L, Pernet D, MacCrimmon S, Goodwin L, et al. Mental health outcomes at the end of the British involvement in the Iraq and Afghanistan conflicts: a cohort study. The British Journal of Psychiatry. 2018;213(6):690-7.
9. Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. Depression and anxiety. 2011;28(7):596-606.

CHAPTER 3 SUPPLEMENTARY MATERIALS 2: INJURY TYPES STRATIFIED BY AMPUTATION/NON-AMPUTATION INJURY GROUPS



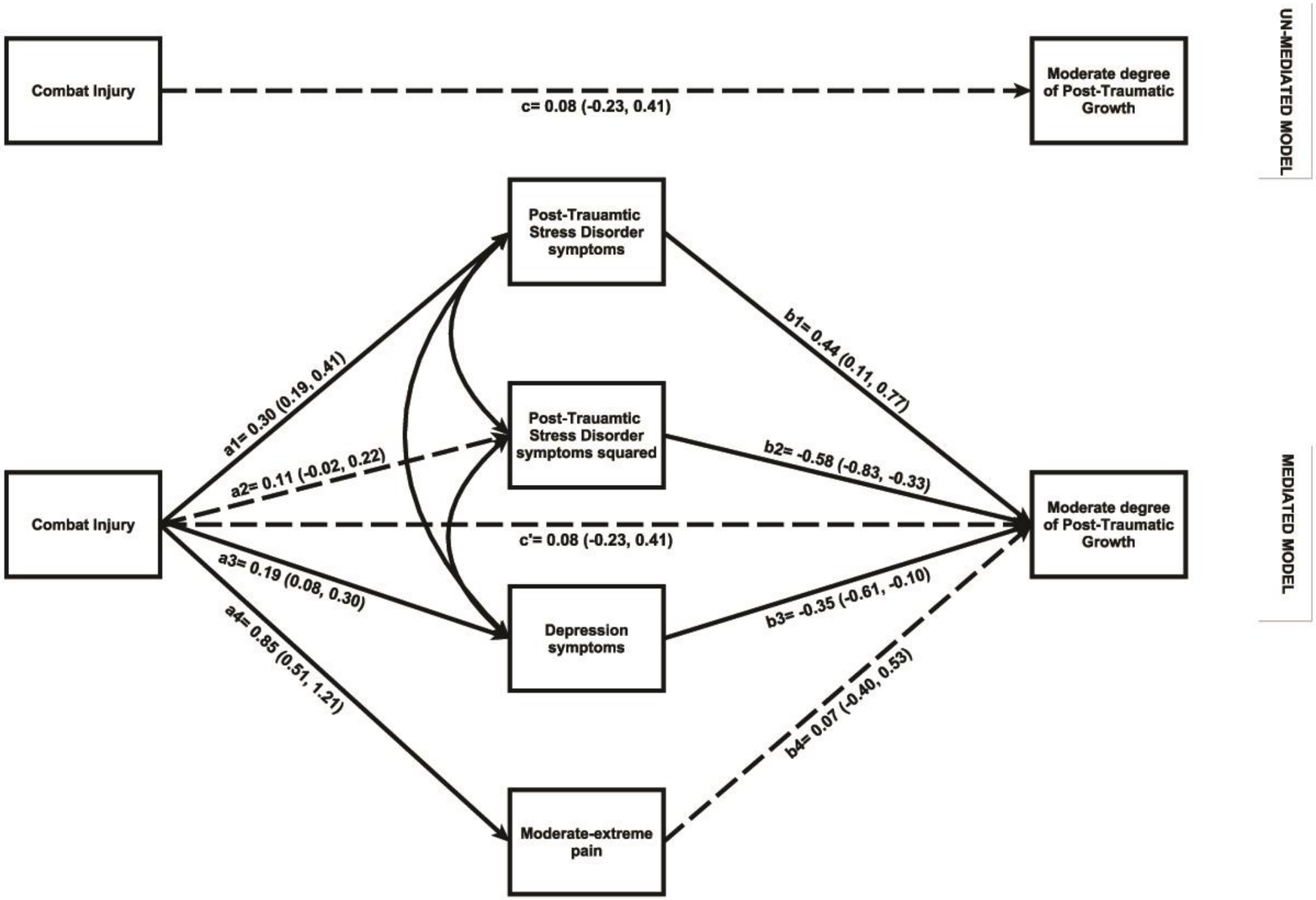
***Participants may have injuries on multiple areas of the body or multiple limbs amputated. Participants may experience a mixture of blast, gunshot and/or other mechanisms of injury.**

CHAPTER 3 SUPPLEMENTARY MATERIALS 3: REGRESSION ANALYSIS WITHOUT BOOTSTRAP

	OR (95%CI)	AOR* (95%CI)
Injury status: Overall Injured Group *(ref: uninjured)*		
PTSD (PCL-C ≥50)	**1·77 (1·23, 2·54)**	**1·67 (1·15, 2·41)**
Depression (PHQ9 ≥10)	**1·58 (1·17, 2·13)**	**1·46 (1·07, 2·00)**
Anxiety (GAD7 ≥10)	**1·65 (1·19, 2·28)**	**1·56 (1·12, 2·19)**
Mental health multimorbidity (caseness on PCL & PHQ9 or GAD7)	**1·71 (1·18, 2·49)**	**1·62 (1·10, 2·37)**
Injury status: Injured-Amputation subgroup *(ref: uninjured)*		
PTSD (PCL-C ≥50)	**1·00 (0·55, 1·83)**	**0·92 (0·50, 1·69)**
Depression (PHQ9 ≥10)	**1·02 (0·63, 1·65)**	**0·87 (0·52, 1·45)**
Anxiety (GAD7 ≥10)	**1·05 (0·62, 1·77)**	**0·97 (0·57, 1·66)**
Mental health multimorbidity (caseness on PCL & PHQ9 or GAD7)	**0·85 (0·44, 1·64)**	**0·77 (0·40, 1·51)**
Injury status: Injured-Non-amputation injury subgroup *(ref: uninjured)*		
PTSD (PCL-C ≥50)	**2·09 (1·43, 3·05)**	**2·01 (1·37, 2·96)**
Depression (PHQ9 ≥10)	**1·82 (1·32, 2·50)**	**1·74 (1·25, 2·43)**
Anxiety (GAD7 ≥10)	**1·91 (1·36, 2·68)**	**1·83 (1·28, 2·60)**
Mental health multimorbidity (caseness on PCL & PHQ9 or GAD7)	**2·08 (1·41, 3·07)**	**2·00 (1·34, 2·98)**
Injury status: Injured-Amputation subgroup *(ref: injured non-amputation injury subgroup)*		
PTSD (PCL-C ≥50)	**0·48 (0·27, 0·86)**	**0·45 (0·25, 0·81)**
Depression (PHQ9 ≥10)	**0·56 (0·35, 0·90)**	**0·49 (0·29, 0·81)**

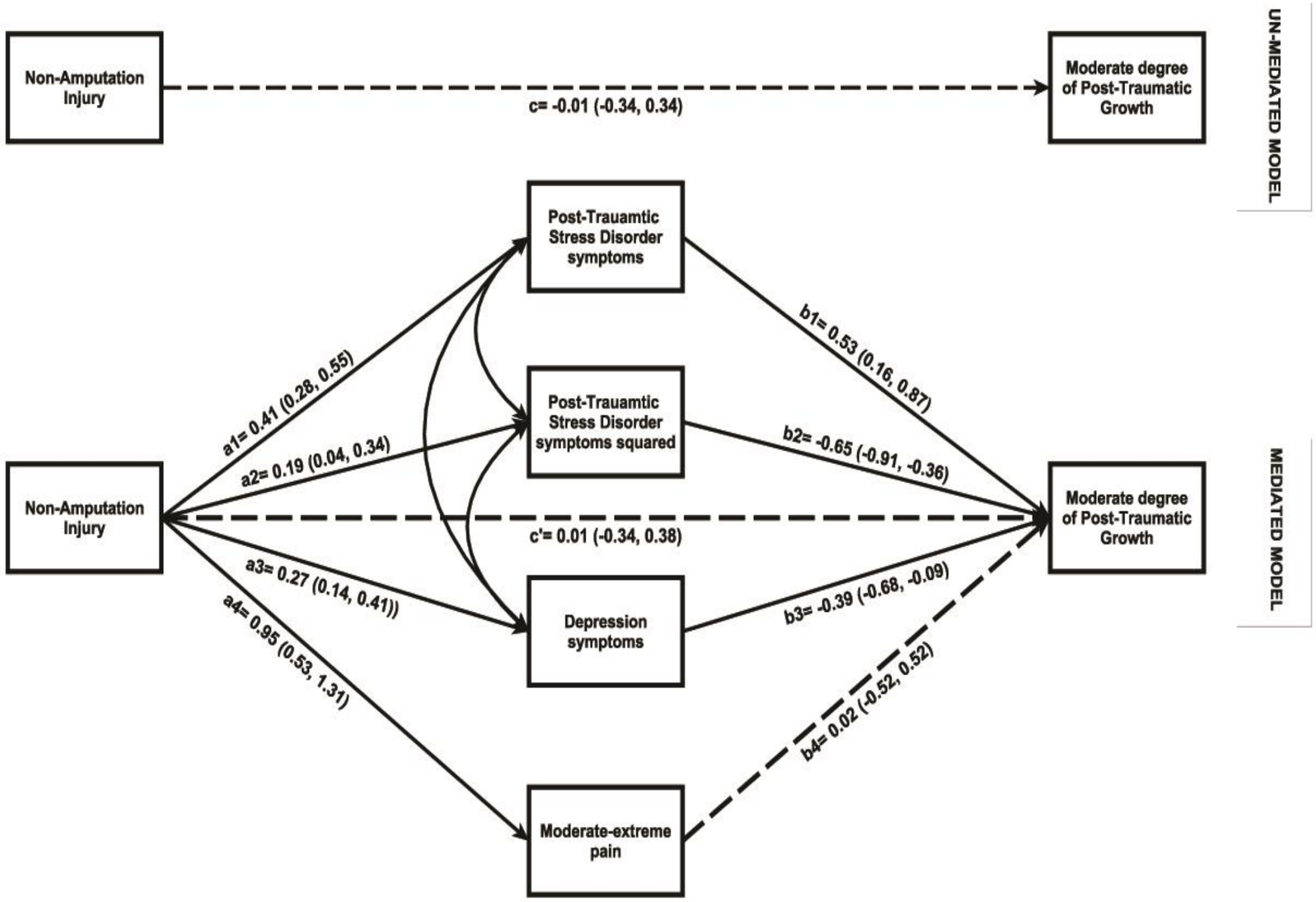
	OR (95%CI)	**AOR* (95%CI)**
Anxiety (GAD7 ≥10)	**0·55 (0·33, 0·92)**	**0·52 (0·31, 0·88)**
Mental health multimorbidity (caseness on PCL & PHQ9 or GAD7)	**0·41 (0·22, 0·78)**	**0·38 (0·20, 0·73)**
***Adjusted for socioeconomic status and age. Officers excluded.**		

CHAPTER 4 SUPPLEMENTARY MATERIALS 1: GENERALISED STRUCTURAL EQUATION MODEL ASSESSING THE RELATIONSHIP BETWEEN COMBAT INJURED GROUP (*V.* UNINJURED GROUP) AND REPORTING A LARGE DEGREE OF PTG, MEDIATED BY PTSD SYMPTOMS, PTSD SYMPTOMS^2, DEPRESSION AND PAIN.



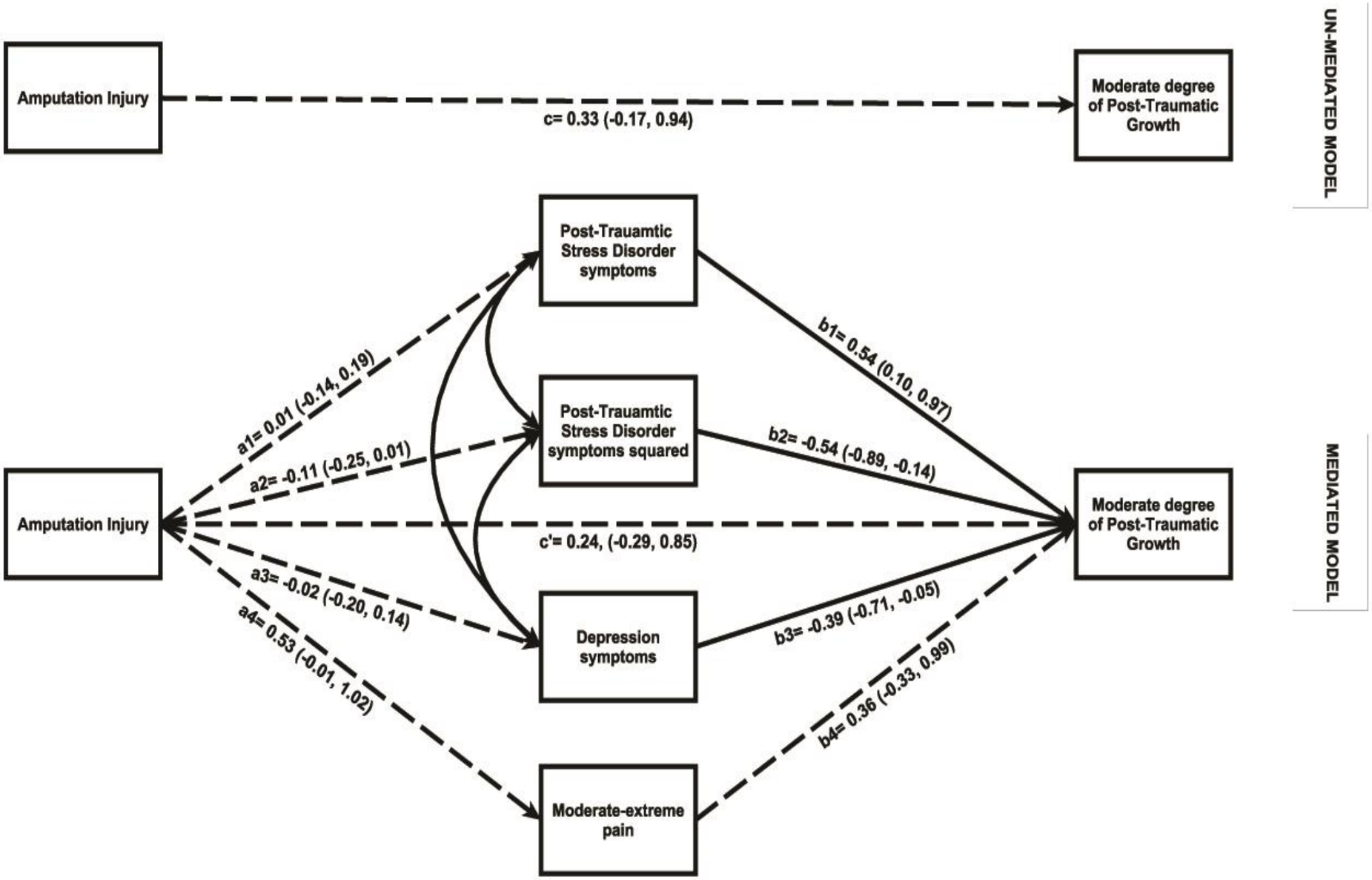
Model adjusted for age at ADVANCE assessment, rank at sampling and time since sampled deployment/injury to completing the DPTGI. Standardised coefficients and 95% confidence intervals shown. Confidence intervals that suggest non-significant associations are denoted as dotted lines.

CHAPTER 4 SUPPLEMENTARY MATERIALS 2: GENERALISED STRUCTURAL EQUATION MODEL ASSESSING THE RELATIONSHIP BETWEEN NON-AMPUTATION INJURED SUBGROUP (*V.* UNINJURED GROUP) AND REPORTING A LARGE DEGREE OF PTG, MEDIATED BY PTSD SYMPTOMS, PTSD SYMPTOMS^2, DEPRESSION AND PAIN.



Model adjusted for age at ADVANCE assessment, rank at sampling and time since sampled deployment/injury to completing the DPTGI. Standardised coefficients and 95% confidence intervals shown. Confidence intervals that suggest non-significant associations are denoted as dotted lines.

CHAPTER 4 SUPPLEMENTARY MATERIALS 3: GENERALISED STRUCTURAL EQUATION MODEL ASSESSING THE RELATIONSHIP BETWEEN AMPUTATION INJURED SUBGROUP (*V.* UNINJURED GROUP) AND REPORTING A LARGE DEGREE OF PTG, MEDIATED BY PTSD SYMPTOMS, PTSD SYMPTOMS^2, DEPRESSION AND PAIN.



Model adjusted for age at ADVANCE assessment, rank at sampling and time since sampled deployment/injury to completing the DPTGI. Standardised coefficients and 95% confidence intervals shown. Confidence intervals that suggest non-significant associations are denoted as dotted lines.

CHAPTER 5 SUPPLEMENTARY MATERIALS 1: CLASSIFICATION OF NORMAL RANGES FOR CARDIOVASCULAR OUTCOMES

Outcome	Range	Reference
Cholesterol (total)	**Desirable: <200mg/dl** **Borderline high: 200-239mg/dl** **High: ≥240mg/dl**	**National Institutes of Health. (2001). ATP III guidelines at-a-glance quick desk reference. *NIH publication*, 01-3305.**
Diastolic blood pressure	**Normal: <80mmHg** **Prehypertensive: 80-89 mmHg** **Stage 1 hypertension 90-99 mmHg** **Stage 2 hypertension ≥100 mmHg**	**Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo Jr, J. L., ... & National High Blood Pressure Education Program Coordinating Committee. (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Jama*, *289*(19), 2560-2571.**
Estimated Glucose Disposal Rate (Insulin Resistance)	**Indicative of metabolic syndrome: ≤8.77mg/kg/min**	**Chillaron, J. J., Goday, A., Flores-Le-Roux, J. A., Benaiges, D., Carrera, M. J., Puig, J., ... & Pedro-Botet, J. (2009). Estimated glucose disposal rate in assessment of the metabolic syndrome and microvascular complications in patients with type 1 diabetes. *The journal of clinical endocrinology & metabolism*, *94*(9), 3530-3534.**
$HbA1_C$	**Normal: <42mmol/mol**	**The International Expert Committee. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327–34**
HDL	**Low (risk factor):**	**National Institutes of Health. (2001). ATP**

Outcome	Range	Reference
	<40mg/dl **High (negative risk factor):>60mg/dl**	**III guidelines at-a-glance quick desk reference. *NIH publication*, 01-3305.**
High Sensitivity C-Reactive Protein	**Low risk: <1mg/l** **Average: 1-3mg/l** **High risk: >3mg/l**	**Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon III, R. O., Criqui, M., ... & Vinicor, F. (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *circulation*, *107*(3), 499-511.**
LDL	**Optimal: <100 mg/dl** **Near optimal: 100-129mg/dl** **Borderline high: 130-159mg/dl** **High 160-189mg/dl** **Very high: ≥190mg/dl**	**National Institutes of Health. (2001). ATP III guidelines at-a-glance quick desk reference. *NIH publication*, 01-3305.**
Pulse wave velocity	**Optimal range: 6.6m/s (+2 SD 4.4–8.9)** **Normal range: 6.8m/s (+2 SD 4.2–9.4)** **High normal range: 7.1m/s (+2 SD 4.5–9.7)** **Grade 1 Hypertension range: 7.3m/s (+2 SD 4.0–10.7)** **Grade 2 Hypertension range: 8.2m/s (+2 SD**	**Reference Values for Arterial Stiffness' Collaboration. (2010). Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors:'establishing normal and reference values'. *European heart journal*, *31*(19), 2338-2350.**

Outcome	Range	Reference
	3.3–13.0)	
Resting heart rate	**Normal: 50-80bpm**	**Quer, G., Gouda, P., Galarnyk, M., Topol, E. J., & Steinhubl, S. R. (2020). Inter-and intraindividual variability in daily resting heart rate and its associations with age, sex, sleep, BMI, and time of year: Retrospective, longitudinal cohort study of 92,457 adults. *Plos one*, *15*(2), e0227709.**
Systolic blood pressure	**Normal: <120 mmHg** **Prehypertensive: 120-139 mmHg** **Stage 1 Hypertension: 140-159 mmHg** **Stage 2 Hypertension: ≥160 mmHg**	**Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo Jr, J. L., ... & National High Blood Pressure Education Program Coordinating Committee. (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Jama*, *289*(19), 2560-2571.**
Triglycerides	**Normal: <150mg/dl** **Borderline high: 150-199mg/dl** **High: 200-499mg/dl** **Very high: ≥500mg/dl**	**National Institutes of Health. (2001). ATP III guidelines at-a-glance quick desk reference. *NIH publication*, 01-3305.**
Visceral Adipose Tissue	**Normal: <100cm^2** **Increased risk: 100-160cm^2** **High risk: ≥160cm^2**	**Kelly, T. L. (2010). Practical and technical advantages of DXA visceral fat assessment compared with computed tomography. *Age*, *36*(42.3), 50.**

CHAPTER 5 SUPPLEMENTARY MATERIALS 2: VARIABLE SELECTION PROCEDURE AND ASSOCIATED BOOTSTRAP INCLUSION FREQUENCIES

Outcome group	Outcome	Symptom cluster	Evidence of non-linear relationship	Bootstrap Inclusion Frequencies	Bootstrap Inclusion Frequencies (excluding outliers)	Co-dependence	WALS t-score (1-Std. error bands)	WALS t-score (1-Std. error bands) (excluding outliers)	Multiple symptom model likelihood ratio chi^2 test (*p*-value)	Multiple symptom model likelihood ratio chi^2 test (*p*-value) (excluding outliers)
Inflammation	HsCRP	Avoidance behaviours	No	8.60	15.30	-	-	-	-	-
	HsCRP	Emotional numbing	No	5.30	4.90	-	-	-	-	-
	HsCRP	Hyperarousal	No	7.60	7.00	-	-	-	-	-
	HsCRP	Intrusive thoughts	No	23.20	25.20	-	-	-	-	-
	Diastolic blood pressure	Avoidance behaviours	No	19.70	12.80	-	-	-	-	-
	Diastolic blood pressure	Emotional numbing	No	10.10	9.70	-	-	-	-	-
	Diastolic blood pressure	Hyperarousal	No	13.20	10.70	-	-	-	-	-
	Diastolic blood pressure	Intrusive thoughts	No	13.00	7.30	-	-	-	-	-
	Pulse wave velocity	Avoidance behaviours	No	35.60	19.50	-	1.37 (0.01, 0.04)	0.93 (-0.00, 0.02)	-	-
	Pulse wave velocity	Emotional numbing	No	9.70	4.50	-	-	-	-	-
	Pulse wave velocity	Hyperarousal	No	15.60	8.80	-	-	-	-	-
	Pulse wave velocity	Intrusive thoughts	Yes	13.60 3.90	13.70 3.70	-	-	-	-	-
	Resting heart rate	Avoidance behaviours	No	20.10	11.10	-	-	-	-	-
	Resting heart rate	Emotional numbing	Yes	83.10 56.10	67.50 3.80	-	Term 1: 2.21 (0.24, 0.63) Term 2: -1.72 (-1.48, -0.39)	Term 1: 2.21 (0.07, 0.36) Term 2: -0.50 (-0.56, 0.18)	-	-
	Resting heart rate	Hyperarousal	No	14.50	22.70	-	-	-	-	-
	Resting heart rate	Intrusive thoughts	No	19.10	12.30	-	-	-	-	-
	Systolic blood pressure	Avoidance behaviours	No	32.00	66.40	No	1.36 (0.08, 0.53)	2.61 (0.33, 0.74)		
	Systolic blood pressure	Emotional numbing	No	8.10	16.00	-	-	-	-	-
	Systolic blood pressure	Hyperarousal	Yes	8.40	27.20	-	-	-	-	-

Outcome group	Outcome	Symptom cluster	Evidence of non-linear relationship	Bootstrap Inclusion Frequencies	Bootstrap Inclusion Frequencies (excluding outliers)	Co-dependence	WALS t-score (1-Std. error bands)	WALS t-score (1-Std. error bands) (excluding outliers)	Multiple symptom model likelihood ratio chi^2 test (*p*-value)	Multiple symptom model likelihood ratio chi^2 test (*p*-value) (excluding outliers)
				2.60	11.40					
	Systolic blood pressure	Intrusive thoughts	Yes	33.20 11.00	62.60 15.00	No	Term 1: 1.02 (0.01, 0.55) Term 2: -1.52 (-3.09, -0.63)	Term 1: 1.34 (0.09, 0.63) Term 2: -2.55 (-4.01, -1.75)	-	-
Cardiometabolic effects	Cholesterol (total)	Avoidance behaviours	No	12.10	4.30	-	-	-	-	-
	Cholesterol (total)	Emotional numbing	No	14.50	4.90	-	-	-	-	-
	Cholesterol (total)	Hyperarousal	No	11.80	8.20	-	-	-	-	-
	Cholesterol (total)	Intrusive thoughts	No	16.50	3.40	-	-	-	-	-
	$HbA1_C$	Avoidance behaviours	No	6.00	8.70	-	-	-	-	-
	$HbA1_C$	Emotional numbing	No	3.10	14.10	-	-	-	-	-
	$HbA1_C$	Hyperarousal	No	8.00	6.40	-	-	-	-	-
	$HbA1_C$	Intrusive thoughts	No	9.30	1.20	-	-	-	-	-
	High-Density Lipoproteins	Avoidance behaviours	No	19.70	16.70	-	-	-	-	-
	High-Density Lipoproteins	Emotional numbing	No	19.60	19.60	-	-	-	-	-
	High-Density Lipoproteins	Hyperarousal	No	13.30	31.40	No	0.15 (-0.07, 0.09)	-1.14 (-0.14, -0.01)	1.39 (0.24)	0.40 (0.52)
	High-Density Lipoproteins	Intrusive thoughts	No	33.50	28.00	No	-1.05 (-0.19, -0.00)	-0.85 (-0.13, 0.01)	0.04 (0.85)	1.04 (0.31)
	Insulin resistance	Avoidance behaviours	No	7.60	22.20	-	-	-	-	-
	Insulin resistance	Emotional numbing	No	8.10	46.00	No	-0.48 (-0.01, 0.01)	-1.77 (-0.02, -0.00)	0.29 (0.59)	1.55 (0.21)
	Insulin resistance	Hyperarousal	No	17.90	23.90	-	-	-	-	-

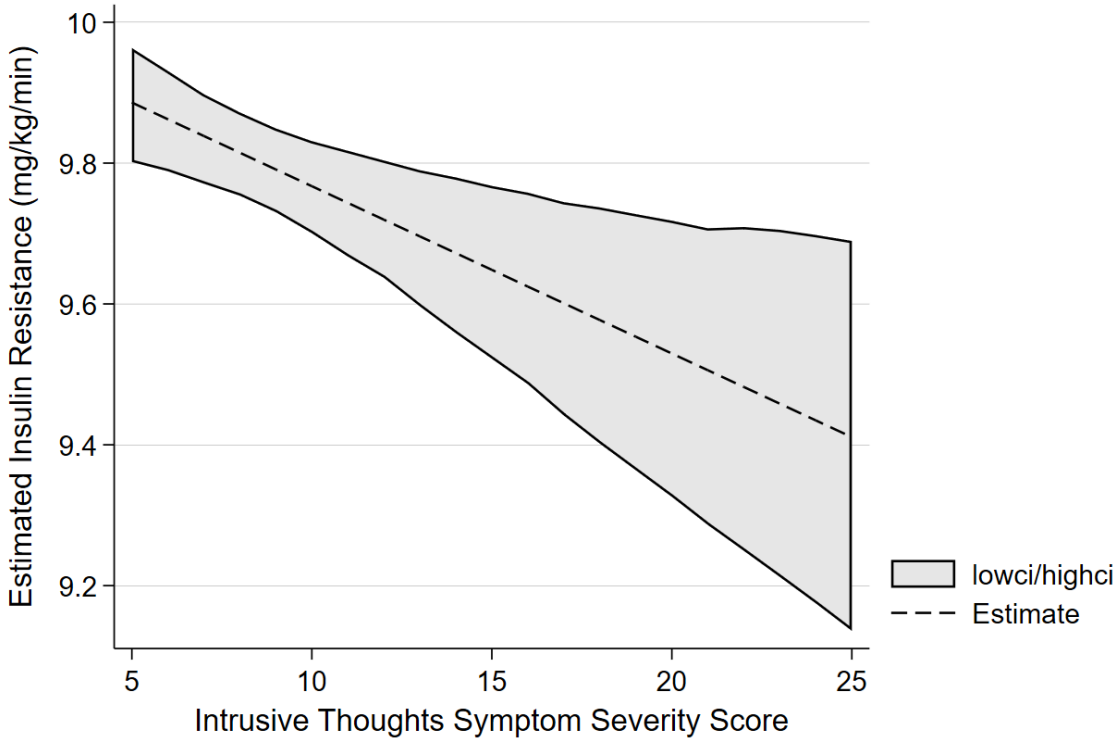
Outcome group	Outcome	Symptom cluster	Evidence of non-linear relationship	Bootstrap Inclusion Frequencies	Bootstrap Inclusion Frequencies (excluding outliers)	Co-dependence	WALS t-score (1-Std. error bands)	WALS t-score (1-Std. error bands) (excluding outliers)	Multiple symptom model likelihood ratio chi^2 test (*p*-value)	Multiple symptom model likelihood ratio chi^2 test (*p*-value) (excluding outliers)
	Insulin resistance	**Intrusive thoughts**	**No**	**10.50**	**39.40**	**No**	**-0.27 (-0.01, 0.00)**	**-1.42 (-0.02, -0.00)**	**0.06 (0.81)**	**2.39 (0.12)**
	Low-Density Lipoproteins	**Avoidance behaviours**	**No**	**30.70**	**14.70**	**-**	**0.99 (-0.00, 1.13)**	**0.70 (-0.15, 0.83)**	**-**	**-**
	Low-Density Lipoproteins	**Emotional numbing**	**No**	**30.20**	**11.60**	**No**	**1.23 (0.08, 0.74)**	**0.79 (-0.05, 0.46)**	**5.39 (0.02)**	**3.59 (0.06)**
	Low-Density Lipoproteins	**Hyperarousal**	**No**	**58.10**	**43.80**	**No**	**-2.24 (-0.90, -0.35)**	**-1.84 (-0.66, -0.20)**	**3.74 (0.05)**	**1.34 (0.25)**
	Low-Density Lipoproteins	**Intrusive thoughts**	**No**	**15.50**	**10.40**	**-**	**-**	**-**	**-**	**-**
	Trigylcerides	**Avoidance behaviours**		**10.40**	**12.30**	**-**	**-**	**-**	**-**	**-**
	Trigylcerides	**Emotional numbing**	**No**	**18.20**	**17.80**	**-**	**-**	**-**	**-**	**-**
	Trigylcerides	**Hyperarousal**	**No**	**50.30**	**56.70**	**-**	**1.91 (0.00, 0.01)**	**2.56 (0.00, 0.01)**	**-**	**-**
	Trigylcerides	**Intrusive thoughts**	**No**	**19.60**	**25.70**	**-**	**-**	**-**	**-**	**-**
	Visceral Adipose Tissue	**Avoidance behaviours**	**No**	**10.80**	**16.20**	**-**	**-**	**-**	**-**	**-**
	Visceral Adipose Tissue	**Emotional numbing**	**No**	**17.50**	**11.30**	**-**	**-**	**-**	**-**	**-**
	Visceral Adipose Tissue	**Hyperarousal**	**No**	**28.50**	**11.00**	**-**	**-**	**-**	**-**	**-**
	Visceral Adipose Tissue	**Intrusive thoughts**	**No**	**18.40**	**37.10**	**-**	**1.49 (0.11, 0.54)**	**1.81 (0.15, 0.51)**	**-**	**-**
Acronyms: BIF Bootstrap Inclusion Frequency WALS Weighted Absolute Least Squares										

CHAPTER 5 SUPPLEMENTARY MATERIALS 3: SPEARMAN CORRELATIONS BETWEEN PTSD SYMPTOMS AND CARDIOVASCULAR RISK OUTCOMES

	PCL-Hyperarousal	PCL-Intrusive thought	PCL-Emotional Numbing	PCL-Avoidance behaviour	Age at assessment	Sampling rank	Combat injury	Medication	Heart rate	Diastolic blood pressure	Systolic blood pressure	Pulse wave velocity	Cholesterol	HDL	LDL	Triglycerides (log)	$HbA1_C$	Insulin resistance	Visceral Adipose Tissue	HsCRP (log)
PCL-Hyperarousal	**1.00**																			
PCL-Intrusive thought	**0.69**	**1.00**																		
PCL-Emotional Numbing	**0.77**	**0.64**	**1.00**																	
PCL-Avoidance behaviour	**0.58**	**0.71**	**0.61**	**1.00**																
Age at assessment	**0.01**	**-0.01**	**-0.02**	**0.02**	**1.00**															
Sampling rank	**-0.18**	**-0.13**	**-0.17**	**-0.09**	**0.47**	**1.00**														
Combat injury	**0.18**	**0.13**	**0.25**	**0.09**	**-0.04**	**-0.10**	**1.00**													
Medication	**0.21**	**0.20**	**0.22**	**0.17**	**0.05**	**-0.05**	**0.05**	**1.00**												
Heart rate	**0.09**	**0.08**	**0.15**	**0.08**	**0.00**	**-0.14**	**0.13**	**0.11**	**1.00**											
Diastolic blood pressure	**0.01**	**0.01**	**-0.01**	**0.00**	**0.18**	**0.08**	**-0.04**	**0.11**	**0.22**	**1.00**										
Systolic blood pressure	**0.07**	**0.07**	**0.04**	**0.09**	**0.19**	**-0.02**	**-0.02**	**0.11**	**0.13**	**0.54**	**1.00**									
Pulse wave	**0.08**	**0.08**	**0.07**	**0.10**	**0.12**	**0.02**	**0.00**	**0.05**	**0.04**	**0.07**	**0.17**	**1.00**								

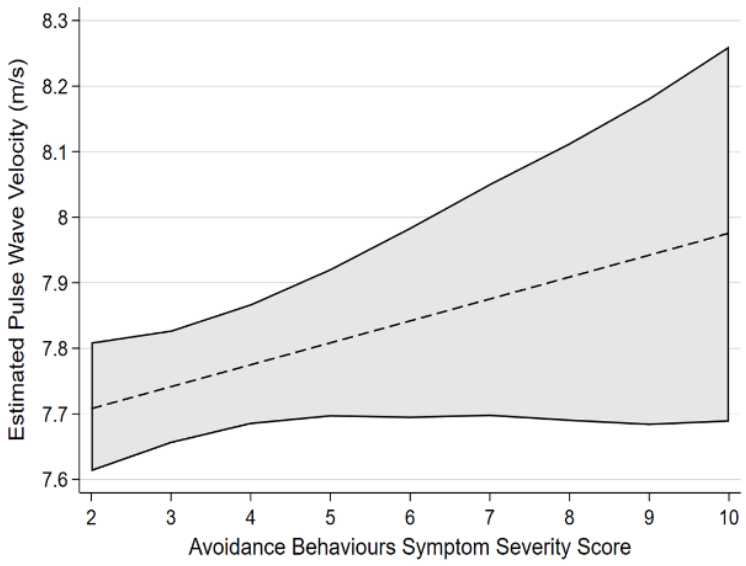
	PCL-Hyperarousal	PCL-Intrusive thought	PCL-Emotional Numbing	PCL-Avoidance behaviour	Age at assessment	Sampling rank	Combat injury	Medication	Heart rate	Diastolic blood pressure	Systolic blood pressure	Pulse wave velocity	Cholesterol	HDL	LDL	Triglycerides (log)	$HbA1_C$	Insulin resistance	Visceral Adipose Tissue	HsCRP (log)
velocity																				
Cholesterol	**-0.04**	**-0.05**	**-0.04**	**-0.01**	**0.24**	**0.16**	**-0.04**	**-0.01**	**0.10**	**0.20**	**0.13**	**0.00**	**1.00**							
HDL	**-0.10**	**-0.08**	**-0.10**	**-0.02**	**0.13**	**0.14**	**-0.08**	**-0.08**	**-0.18**	**-0.10**	**0.02**	**0.08**	**0.20**	**1.00**						
LDL	**-0.06**	**-0.07**	**-0.06**	**-0.02**	**0.19**	**0.13**	**-0.05**	**-0.04**	**0.08**	**0.15**	**0.08**	**-0.01**	**0.93**	**0.00**	**1.00**					
Triglycerides (log)	**0.14**	**0.12**	**0.13**	**0.09**	**0.13**	**0.03**	**0.08**	**0.15**	**0.26**	**0.27**	**0.17**	**0.02**	**0.39**	**-0.33**	**0.26**	**1.00**				
$HbA1_C$	**-0.01**	**0.01**	**0.00**	**0.02**	**0.14**	**0.03**	**-0.10**	**0.06**	**-0.03**	**0.12**	**0.04**	**-0.03**	**0.17**	**-0.01**	**0.17**	**0.10**	**1.00**			
Insulin resistance	**-0.12**	**-0.11**	**-0.12**	**-0.10**	**-0.25**	**-0.04**	**-0.07**	**-0.21**	**-0.21**	**-0.31**	**-0.29**	**-0.08**	**-0.18**	**0.25**	**-0.18**	**-0.38**	**-0.20**	**1.00**		
Visceral Adipose Tissue	**0.13**	**0.10**	**0.11**	**0.09**	**0.32**	**0.02**	**0.10**	**0.16**	**0.26**	**0.28**	**0.29**	**0.06**	**0.19**	**-0.26**	**0.17**	**0.45**	**0.04**	**-0.73**	**1.00**	
HsCRP (log)	**0.05**	**0.06**	**0.06**	**0.01**	**0.01**	**-0.09**	**0.06**	**0.10**	**0.17**	**0.18**	**0.14**	**-0.02**	**0.03**	**-0.22**	**0.06**	**0.18**	**0.10**	**-0.36**	**0.34**	**1.00**

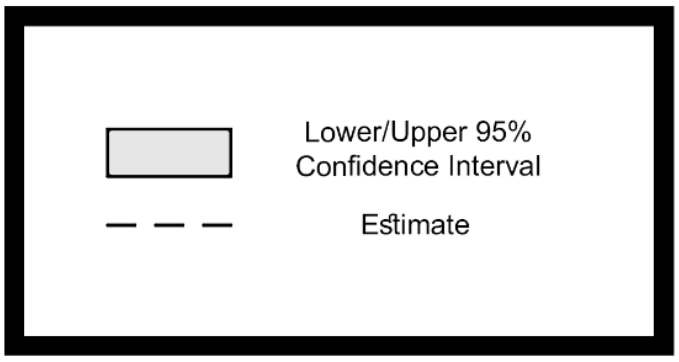
CHAPTER 5 SUPPLEMENTARY MATERIALS 4: ESTIMATED MARGINAL EFFECTS OF THE INTRUSIVE THOUGHTS SYMPTOM CLUSTER SELECTED FOR THE INSULIN RESISTANCE MODEL BY VARIABLE SELECTION PROCEDURES AND CONFIRMED BY ROBUST REGRESSION MODELLING, EXCLUDING AGE AS A COVARIATE



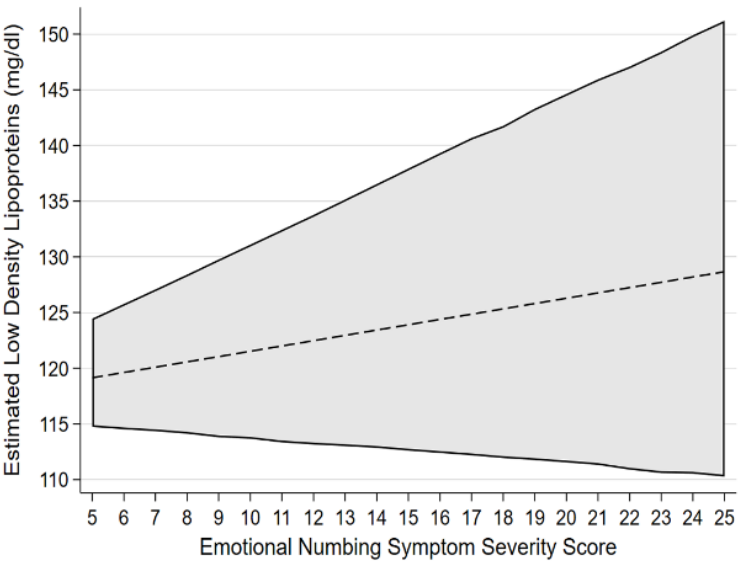
CHAPTER 5 SUPPLEMENTARY MATERIALS 5: ESTIMATED MARGINAL EFFECTS OF PTSD FACTORS ASSOCIATED WITH CARDIOVASCULAR RISK OUTCOMES, NOT CONFIRMED IN ROBUST REGRESSION MODEL

AVOIDANCE BEHAVIOURS

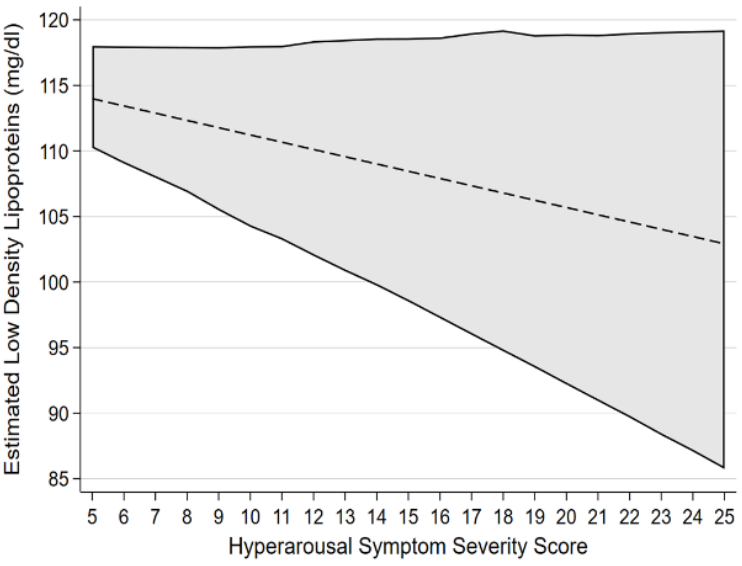


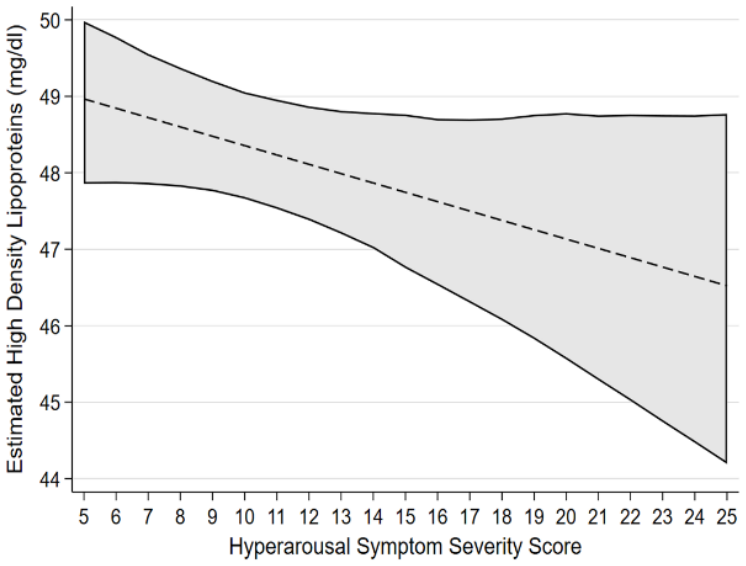


EMOTIONAL NUMBING

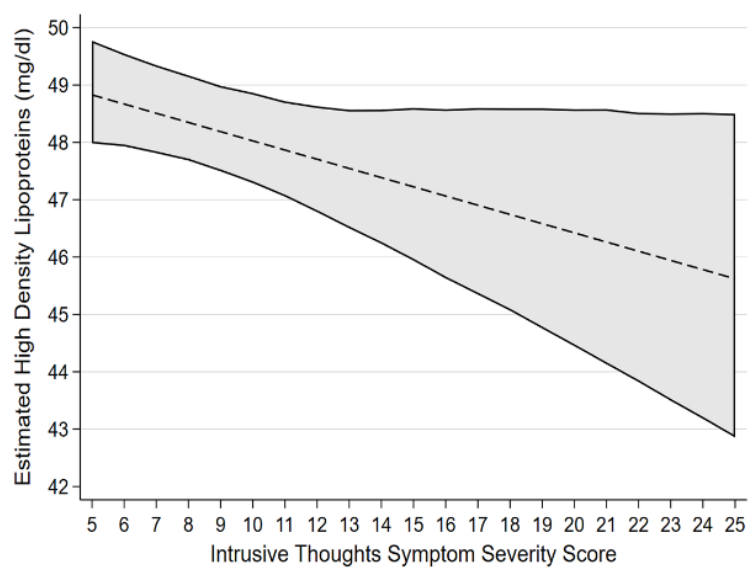


HYPERAROUSAL





INTRUSIVE THOUGHTS



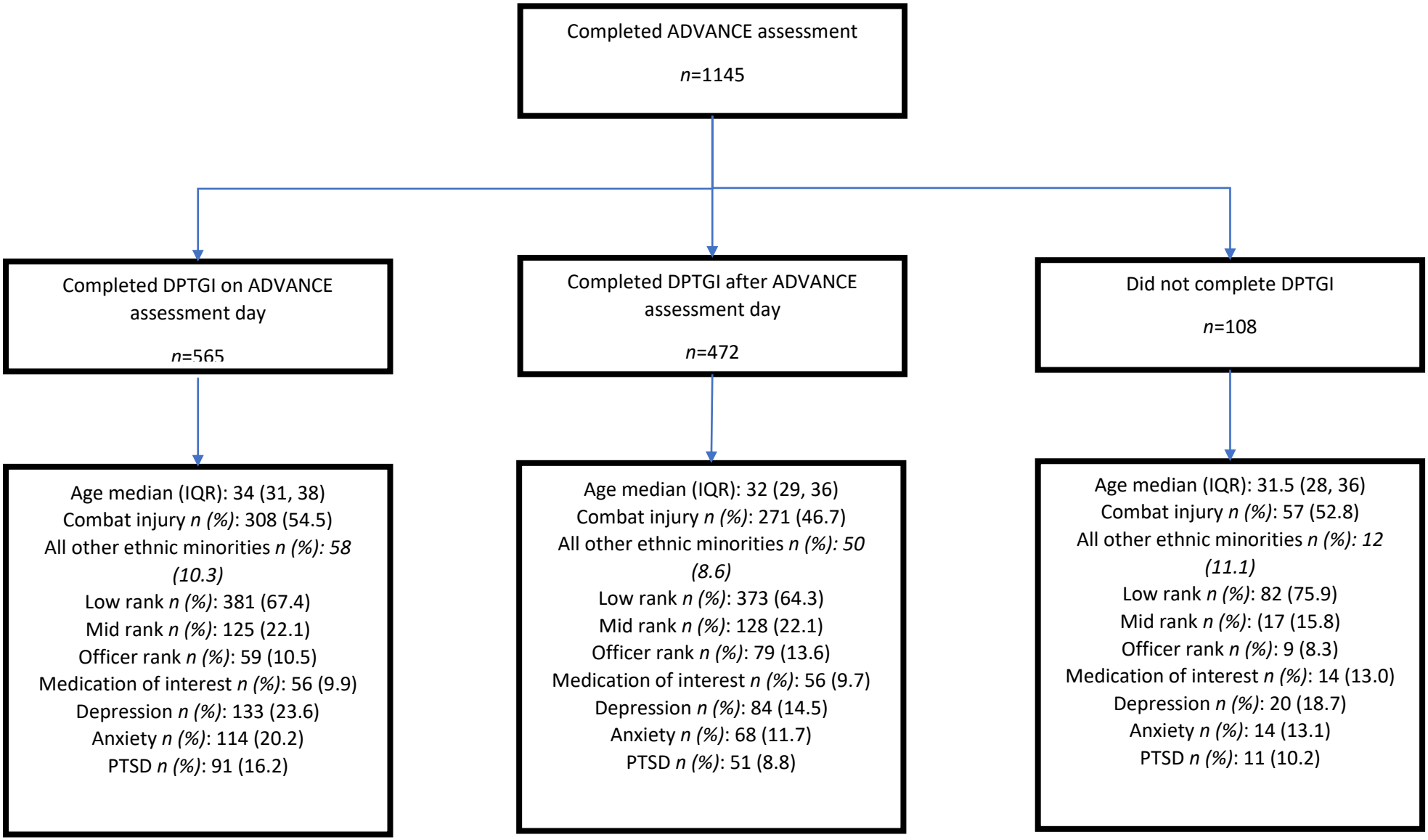
CHAPTER 6 SUPPLEMENTARY MATERIALS 1: CLASSIFICATION OF NORMAL RANGES FOR CARDIOVASCULAR OUTCOMES

Outcome	Range	Reference
Cholesterol (total)	**Desirable: <200mg/dl** **Borderline high: 200-239mg/dl** **High: ≥240mg/dl**	**National Institutes of Health. (2001). ATP III guidelines at-a-glance quick desk reference. *NIH publication*, 01-3305.**
Diastolic blood pressure	**Normal: <80mmHg** **Prehypertensive: 80-89 mmHg** **Stage 1 hypertension 90-99 mmHg** **Stage 2 hypertension ≥100 mmHg**	**Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo Jr, J. L., ... & National High Blood Pressure Education Program Coordinating Committee. (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Jama*, *289*(19), 2560-2571.**
Estimated Glucose Disposal Rate (Insulin Resistance)	**Indicative of metabolic syndrome: ≤8.77mg/kg/min**	**Chillaron, J. J., Goday, A., Flores-Le-Roux, J. A., Benaiges, D., Carrera, M. J., Puig, J., ... & Pedro-Botet, J. (2009). Estimated glucose disposal rate in assessment of the metabolic syndrome and microvascular complications in patients with type 1 diabetes. *The journal of clinical endocrinology & metabolism*, *94*(9), 3530-3534.**
HbA1c	**Normal: <42mmol/mol**	**The International Expert Committee. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327–34**
HDL	**Low (risk factor): <40mg/dl**	**National Institutes of Health. (2001). ATP III guidelines at-a-glance**

Outcome	Range	Reference
	High (negative risk factor):>60mg/dl	**quick desk reference. *NIH publication*, 01-3305.**
High Sensitivity C-Reactive Protein	**Low risk: <1mg/l** **Average: 1-3mg/l** **High risk: >3mg/l**	**Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon III, R. O., Criqui, M., ... & Vinicor, F. (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *circulation*, *107*(3), 499-511.**
LDL	**Optimal: <100 mg/dl** **Near optimal: 100-129mg/dl** **Borderline high: 130-159mg/dl** **High 160-189mg/dl** **Very high: ≥190mg/dl**	**National Institutes of Health. (2001). ATP III guidelines at-a-glance quick desk reference. *NIH publication*, 01-3305.**
Pulse wave velocity	**Optimal range: 6.6m/s (+2 SD 4.4–8.9)** **Normal range: 6.8m/s (+2 SD 4.2–9.4)** **High normal range: 7.1m/s (+2 SD 4.5–9.7)** **Grade 1 Hypertension range: 7.3m/s (+2 SD 4.0–10.7)** **Grade 2 Hypertension range:**	**Reference Values for Arterial Stiffness' Collaboration. (2010). Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors:'establishing normal and reference values'. *European heart journal*, *31*(19), 2338-2350.**

Outcome	Range	Reference
	8.2m/s (+2 SD 3.3–13.0)	
Resting heart rate	**Normal: 50-80bpm**	**Quer, G., Gouda, P., Galarnyk, M., Topol, E. J., & Steinhubl, S. R. (2020). Inter-and intraindividual variability in daily resting heart rate and its associations with age, sex, sleep, BMI, and time of year: Retrospective, longitudinal cohort study of 92,457 adults. *Plos one*, *15*(2), e0227709.**
Systolic blood pressure	**Normal: <120 mmHg** **Prehypertensive: 120-139 mmHg** **Stage 1 Hypertension: 140-159 mmHg** **Stage 2 Hypertension: ≥160 mmHg**	**Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo Jr, J. L., ... & National High Blood Pressure Education Program Coordinating Committee. (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Jama*, *289*(19), 2560-2571.**
Triglycerides	**Normal: <150mg/dl** **Borderline high: 150-199mg/dl** **High: 200-499mg/dl** **Very high: ≥500mg/dl**	**National Institutes of Health. (2001). ATP III guidelines at-a-glance quick desk reference. *NIH publication*, 01-3305.**
Visceral Adipose Tissue	**Normal: <100cm^2** **Increased risk: 100-160cm^2** **High risk: ≥160cm^2**	**Kelly, T. L. (2010). Practical and technical advantages of DXA visceral fat assessment compared with computed tomography. *Age*, *36*(42.3), 50.**

CHAPTER 6 SUPPLEMENTARY MATERIALS 2: BREAKDOWN OF ADVANCE STUDY PARTICIPANTS WHO DID/DID NOT COMPLETE THE DEPLOYMENT RELATED POST TRAUMATIC GROWTH INVENTORY



CHAPTER 6 SUPPLEMENTARY MATERIALS 3: SPEARMAN CORRELATION MATRIX BETWEEN POST-TRAUMATIC GROWTH SCORES, METABOLIC EFFECTS, INFLAMMATION, HAEMODYNAMIC FUNCTIONING AND CONFOUNDERS

	PTG: DPTGI-Appreciation of life	PTG: DPTGI-New possibilities	PTG: DPTGI-Personal Strength	PTG: DPTGI-Relating to others	PTG: DPTGI-Spiritual Change	Anxiety-GAD case	Depression-PHQ case	PTSD-PCL case	Age at assessment	Combat injury	Medication	Socioeconomic status	Diastolic blood pressure	Heart rate	Systolic blood pressure	Pulse wave velocity	HsCRP	Cholesterol	HbA1C	HDL	Insulin resistance	LDL	Triglycerides	Visceral Fat
PTG: DPTGI-Appreciation of life	**1.00**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PTG: DPTGI-New possibilities	**0.67**	**1.00**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PTG: DPTGI-Personal Strength	**0.67**	**0.72**	**1.00**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PTG: DPTGI-Relating to others	**0.69**	**0.70**	**0.66**	**1.00**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PTG: DPTGI-Spiritual Change	**0.40**	**0.42**	**0.39**	**0.48**	**1.00**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiety-GAD case	**-0.16**	**-0.10**	**-0.12**	**-0.10**	**-0.03**	**1.00**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Depression-PHQ case	**-0.24**	**-0.16**	**-0.17**	**-0.18**	**-0.08**	**0.60**	**1.00**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

	PTG: DPTGI-Appreciation of life	PTG: DPTGI-New possibilities	PTG: DPTGI-Personal Strength	PTG: DPTGI-Relating to others	PTG: DPTGI-Spiritual Change	Anxiety-GAD case	Depression-PHQ case	PTSD-PCL case	Age at assessment	Combat injury	Medication	Socioeconomic status	Diastolic blood pressure	Heart rate	Systolic blood pressure	Pulse wave velocity	HsCRP	Cholesterol	HbA1C	HDL	Insulin resistance	LDL	Triglycerides	Visceral Fat
PTSD-PCL case	**-0.15**	**-0.06**	**-0.07**	**-0.09**	**-0.03**	**0.63**	**0.62**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Age at assessment	**0.00**	**-0.10**	**-0.10**	**0.00**	**0.03**	**-0.02**	**0.00**	**-0.02**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Combat injury	**0.05**	**0.21**	**0.06**	**0.08**	**0.09**	**0.11**	**0.11**	**0.08**	**-0.06**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Medication	**-0.09**	**-0.04**	**-0.09**	**-0.01**	**0.02**	**0.31**	**0.27**	**0.28**	**0.06**	**0.07**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Socioeconomic status	**0.05**	**-0.15**	**-0.10**	**-0.03**	**-0.04**	**-0.16**	**-0.14**	**-0.16**	**0.47**	**-0.12**	**-0.06**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Diastolic blood pressure	**-0.10**	**-0.08**	**-0.11**	**-0.03**	**-0.01**	**0.01**	**0.01**	**-0.02**	**0.20**	**-0.05**	**0.08**	**0.10**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Heart rate	**-0.06**	**0.00**	**-0.02**	**-0.05**	**-0.02**	**0.14**	**0.14**	**0.12**	**0.00**	**0.15**	**0.12**	**-0.14**	**0.22**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Systolic blood pressure	**-0.04**	**-0.06**	**-0.04**	**-0.01**	**-0.02**	**0.08**	**0.08**	**0.01**	**0.21**	**-0.01**	**0.10**	**-0.01**	**0.54**	**0.14**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Pulse wave velocity	**-0.02**	**-0.07**	**-0.03**	**-0.04**	**-0.06**	**0.04**	**0.08**	**0.04**	**0.11**	**0.01**	**0.05**	**0.02**	**0.08**	**0.03**	**0.16**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
HsCRP	**0.01**	**0.05**	**0.01**	**0.02**	**0.00**	**0.05**	**0.08**	**0.02**	**0.04**	**0.08**	**0.09**	**-0.07**	**0.17**	**0.18**	**0.16**	**0.01**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Cholesterol	**-0.05**	**-0.10**	**-0.12**	**-0.07**	**0.00**	**-0.04**	**0.03**	**-0.06**	**0.25**	**-0.06**	**-0.02**	**0.17**	**0.21**	**0.10**	**0.13**	**-0.01**	**0.04**	**1.00**	**-**	**-**	**-**	**-**	**-**	**-**
HbA1C	**-0.02**	**-0.03**	**-0.01**	**0.03**	**0.06**	**-0.03**	**-0.03**	**0.00**	**0.18**	**-0.09**	**0.04**	**0.05**	**0.13**	**-0.03**	**0.05**	**-0.02**	**0.07**	**0.19**	**1.00**	**-**	**-**	**-**	**-**	**-**

	PTG: DPTGI-Appreciation of life	PTG: DPTGI-New possibilities	PTG: DPTGI-Personal Strength	PTG: DPTGI-Relating to others	PTG: DPTGI-Spiritual Change	Anxiety-GAD case	Depression-PHQ case	PTSD-PCL case	Age at assessment	Combat injury	Medication	Socioeconomic status	Diastolic blood pressure	Heart rate	Systolic blood pressure	Pulse wave velocity	HsCRP	Cholesterol	HbA1C	HDL	Insulin resistance	LDL	Triglycerides	Visceral Fat
HDL	**0.04**	**-0.07**	**-0.01**	**-0.01**	**0.03**	**-0.14**	**-0.12**	**-0.12**	**0.13**	**-0.07**	**-0.06**	**0.14**	**-0.09**	**-0.18**	**0.01**	**0.05**	**-0.21**	**0.18**	**0.00**	**1.00**	**-**	**-**	**-**	**-**
Insulin resistance	**0.06**	**0.06**	**0.04**	**0.06**	**-0.01**	**-0.08**	**-0.16**	**-0.11**	**-0.25**	**-0.08**	**-0.19**	**-0.05**	**-0.31**	**-0.22**	**-0.32**	**-0.10**	**-0.36**	**-0.18**	**-0.20**	**0.25**	**1.00**	**-**	**-**	**-**
LDL	**-0.03**	**-0.07**	**-0.09**	**-0.06**	**0.01**	**-0.05**	**0.02**	**-0.05**	**0.19**	**-0.07**	**-0.05**	**0.13**	**0.16**	**0.08**	**0.09**	**-0.01**	**0.06**	**0.93**	**0.18**	**-0.02**	**-0.18**	**1.00**	**-**	**-**
Triglycerides	**-0.12**	**-0.04**	**-0.07**	**-0.03**	**-0.04**	**0.12**	**0.14**	**0.13**	**0.14**	**0.08**	**0.15**	**0.03**	**0.27**	**0.25**	**0.17**	**0.01**	**0.17**	**0.39**	**0.12**	**-0.34**	**-0.40**	**0.26**	**1.00**	**-**
Visceral Fat	**-0.04**	**-0.05**	**-0.05**	**-0.03**	**0.01**	**0.10**	**0.16**	**0.07**	**0.33**	**0.10**	**0.16**	**0.02**	**0.27**	**0.25**	**0.30**	**0.07**	**0.36**	**0.19**	**0.05**	**-0.26**	**-0.73**	**0.17**	**0.44**	**1.00**

CHAPTER 6 SUPPLEMENTARY MATERIALS 4: VARIABLE SELECTION PROCEDURES

Outcome group	PTG factor	Outcome	Evidence of non-linear relationship?	Bootstrap Inclusion Frequencies	Bootstrap Inclusion Frequencies (excluding outliers)	Co-dependence?	WALS t-score (1-Std. error bands)	WALS t-score (1-Std. error bands) (excluding outliers)	Multiple symptom model likelihood ratio chi^2 test (*p*-value)	Multiple symptom model likelihood ratio chi^2 test (*p*-value) (excluding outliers)
Inflammation	Appreciation of life	HsCRP	No	7.20	9.20	-	-	-	-	-
	New possibilities	HsCRP	No	20.80	20.20	-	-	-	-	-
	Personal strength	HsCRP	No	8.50	5.80	-	-	-	-	-
	Relating to others	HsCRP	No	6.50	6.10	-	-	-	-	-
	Spiritual change	HsCRP	No	8.10	9.10	-	-	-	-	-
Haemodynamic functioning	Appreciation of life	Diastolic blood pressure	No	53.80	28.10	No	-2.60 (-0.35, -0.16)	-2.03 (-0.25, -0.08)	5.26 (0.02)	4.19 (0.04)
	New possibilities	Diastolic blood pressure	No	13.00	15.00	-	-	-	-	-
	Personal strength	Diastolic blood pressure	No	15.30	25.10	-	-	-	-	-
	Relating to others	Diastolic blood pressure	No	9.20	5.60	-	-	-	-	-
	Spiritual change	Diastolic blood pressure	No	58.00	38.20	No	2.07 (0.16, 0.45)	1.72 (0.09, 0.35)	9.69 (<0.01)	5.80 (0.02)
	Appreciation of life, personal strength and spiritual change	Diastolic blood pressure	NA			-	-	-	-	-
	Appreciation of life	Pulse wave velocity	No	5.40	14.50	-	-	-	-	-
	New possibilities	Pulse wave velocity	No	11.30	23.90	-	-	-	-	-
	Personal strength	Pulse wave velocity	No	8.20	11.30	-	-	-	-	-
	Relating to others	Pulse wave velocity	No	7.50	17.20	-	-	-	-	-
	Spiritual change	Pulse wave velocity	No	26.40	26.50	-	-	-	-	-
	Appreciation of life	Resting heart rate	No	10.20	15.70	-	-	-	-	-
	New possibilities	Resting heart rate	Yes	Term 1: 9.10	Term 1: 18.50	-	-	-	-	-

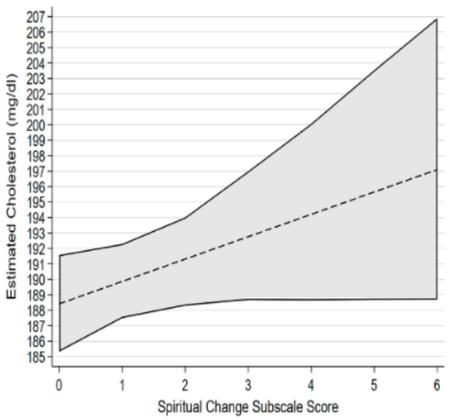
Outcome group	PTG factor	Outcome	Evidence of non-linear relationship?	Bootstrap Inclusion Frequencies	Bootstrap Inclusion Frequencies (excluding outliers)	Co-dependence?	WALS t-score (1-Std. error bands)	WALS t-score (1-Std. error bands) (excluding outliers)	Multiple symptom model likelihood ratio chi^2 test (*p*-value)	Multiple symptom model likelihood ratio chi^2 test (*p*-value) (excluding outliers)
				Term 2: 2.90	Term 2: 7.10					
	Personal strength	Resting heart rate	Yes	23.70 7.60	20.90 8.70	-	-	-	-	-
	Relating to others	Resting heart rate	No	21.30	22.10	-	-	-	-	-
	Spiritual change	Resting heart rate	No	6.90		-	-	-	-	-
	Appreciation of life	Systolic blood pressure	Yes	7.20 1.60	15.20 9.60	-	-	-	-	-
	New possibilities	Systolic blood pressure	Yes	Term 1: 53.00 Term 2: 19.40	Term 1: 50.10 Term 2: 22.90	-	0.75 (-0.04, 0.29) -1.38 (-0.47, -0.07)	0.31 (-0.08, 0.16) -1.15 (-0.30 -0.02)	NA	NA
	Personal strength	Systolic blood pressure	No	8.70	4.60	-	-	-	-	-
	Relating to others	Systolic blood pressure	Yes	6.40 1.40	25.60 12.80	-	-	-	-	-
	Spiritual change	Systolic blood pressure	No	8.80	7.60	-	-	-	-	-
Metabolic effects	Appreciation of life	Cholesterol (total)	Yes	10.80	10.00	-	-	-	-	-
	New possibilities	Cholesterol (total)	No	14.00	11.00	-	-	-	-	-
	Personal strength	Cholesterol (total)	No	24.20	48.30*	Yes	-	-	-	-
	Relating to others	Cholesterol (total)	No	23.90	30.20	No	-1.92 (0.76, 2.36)	-2.28 (-0.59, -0.23)	6.66 (<0.01)	6.30 (0.01)
	Spiritual change	Cholesterol (total)	No	58.60	59.00*	Yes	1.96 (-0.65, -0.21)	2.24 (0.75, 1.96)	4.58 (0.03)	6.31 (0.01)
	Appreciation of life	HbA1c	No	21.00	10.70	-	-	-	-	-
	New possibilities	HbA1c	No	29.70	37.00	-	0.39 (-0.04, 0.08)	-1.34 (-0.05, -0.01)	1.22 (0.27)	10.03 (<0.01)
	Personal strength	HbA1c	No	2.30	7.50	-	-	-	-	-

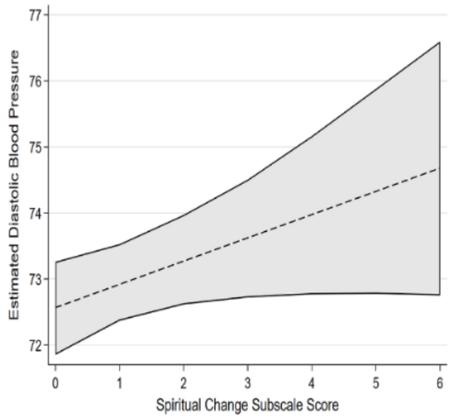
Outcome group	PTG factor	Outcome	Evidence of non-linear relationship?	Bootstrap Inclusion Frequencies	Bootstrap Inclusion Frequencies (excluding outliers)	Co-dependence?	WALS t-score (1-Std. error bands)	WALS t-score (1-Std. error bands) (excluding outliers)	Multiple symptom model likelihood ratio chi^2 test (*p*-value)	Multiple symptom model likelihood ratio chi^2 test (*p*-value) (excluding outliers)
	Relating to others	**HbA1c**	**No**	**5.20**	**18.40**	**-**	**-**	**-**	**-**	**-**
	Spiritual change	**HbA1c**	**No**	**35.10**	**75.60**	**-**	**1.03 (0.00, 0.22)**	**2.48 (0.09, 0.21)**	**0.38 (0.54)**	**2.06 (0.15)**
	Appreciation of life	**High-Density Lipoproteins**	**No**	**29.10**	**64.30**	**-**	**1.36 (0.06, 0.42)**	**2.28 (0.19, 0.48)**	**4.30 (0.04)**	**12.56 (<0.01)**
	New possibilities	**High-Density Lipoproteins**	**No**	**41.40**	**83.70**	**-**	**-1.53 (-0.29, -0.06)**	**-3.00 (-0.39, -0.19)**	**3.42 (0.06)**	**6.38 (0.01)**
	Personal strength	**High-Density Lipoproteins**	**No**	**7.30**	**8.20**	**-**	**-**	**-**	**-**	**-**
	Relating to others	**High-Density Lipoproteins**	**No**	**9.30**	**7.50**	**-**	**-**	**-**	**-**	**-**
	Spiritual change	**High-Density Lipoproteins**	**No**	**8.60**	**8.30**	**-**	**-**	**-**	**-**	**-**
	Appreciation of life	**Insulin resistance**	**No**	**5.50**	**8.40**	**-**	**-**	**-**	**-**	**-**
	New possibilities	**Insulin resistance**	**No**	**11.40**	**16.80**	**-**	**-**	**-**	**-**	**-**
	Personal strength	**Insulin resistance**	**No**	**18.00**	**16.20**	**-**	**-**	**-**	**-**	**-**
	Relating to others	**Insulin resistance**	**No**	**29.30**	**49.50**	**-**	**1.21 (0.00, 0.01)**	**2.02 (0.00, 0.01)**	**4.31 (0.04)**	**1.03 (0.31)**
	Spiritual change	**Insulin resistance**	**No**	**38.30**	**9.60**	**-**	**-1.53 (-0.06, -0.01)**	**-0.76 (-0.03, 0.00)**	**2.21 (0.14)**	**5.21 (0.02)**
	Appreciation of life	**Low-Density Lipoproteins**	**No**	**7.40**	**11.60**	**-**	**-**	**-**	**-**	**-**
	New possibilities	**Low-Density Lipoproteins**	**No**	**11.40**	**14.00**	**-**	**-**	**-**	**-**	**-**
	Personal strength	**Low-Density Lipoproteins**	**No**	**37.00**	**39.20***	**Yes**	**-1.13 (-0.63, -0.04)**	**-1.05 (-0.52, -0.01)**	**NA**	**NA**
	Relating to others	**Low-Density Lipoproteins**	**No**	**19.50**	**35.20**	**-**	**-0.17 -0.20, 0.14)**	**-0.56 (-0.23, 0.07)**	**-**	**-**
	Spiritual change	**Low-Density Lipoproteins**	**No**	**29.00**	**35.90***	**Yes**	**-**	**-**	**-**	**-**
	Personal strength and spiritual change	**Low-Density Lipoproteins**	**No**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
	Personal strength, relating to others and spiritual change	**Low-Density Lipoproteins**	**NA**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
	Appreciation of life	**Trigylcerides**	**No**	**56.90**	**84.20**	**-**	**-2.11 (-0.02, -0.01)**	**-2.81 (-0.02, -0.01)**	**NA**	**NA**

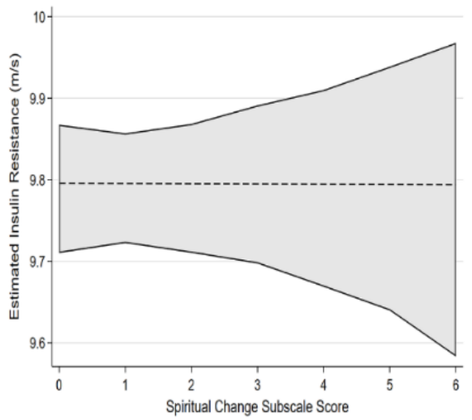
Outcome group	PTG factor	Outcome	Evidence of non-linear relationship?	Bootstrap Inclusion Frequencies	Bootstrap Inclusion Frequencies (excluding outliers)	Co-dependence?	WALS t-score (1-Std. error bands)	WALS t-score (1-Std. error bands) (excluding outliers)	Multiple symptom model likelihood ratio chi^2 test (*p*-value)	Multiple symptom model likelihood ratio chi^2 test (*p*-value) (excluding outliers)
	New possibilities	Trigylcerides	No	14.60	13.40	-	-	-	-	-
	Personal strength	Trigylcerides	No	7.50	12.00	-	-	-	-	-
	Relating to others	Trigylcerides	No	14.50	20.80	-	-	-	-	-
	Spiritual change	Trigylcerides	No	32.30	11.00	-	1.25 (0.00, 0.02)	0.88 (-0.00, 0.01)		-
	Appreciation of life and spiritual change	Triglycerides	No	-	-	-	-	-	-	-
	Appreciation of life	Visceral Adipose Tissue	No	7.20	10.70	-	-	-	-	-
	New possibilities	Visceral Adipose Tissue	No	31.90	16.50	-	-1.43 (-0.54, -0.10)	-1.09 (-0.67, -0.02)	NA	NA
	Personal strength	Visceral Adipose Tissue	No	13.80	8.60	-	-	-	-	-
	Relating to others	Visceral Adipose Tissue	No	10.00	18.10	-	-	-	-	-
	Spiritual change	Visceral Adipose Tissue	No	8.90	8.40	-	-	-	-	-

CHAPTER 6 SUPPLEMENTARY MATERIALS 5: ESTIMATED MARGINAL EFFECTS OF PTG FACTORS ASSOCIATED WITH CARDIOVASCULAR RISK OUTCOMES NOT CONFIRMED IN ROBUST REGRESSION MODELS

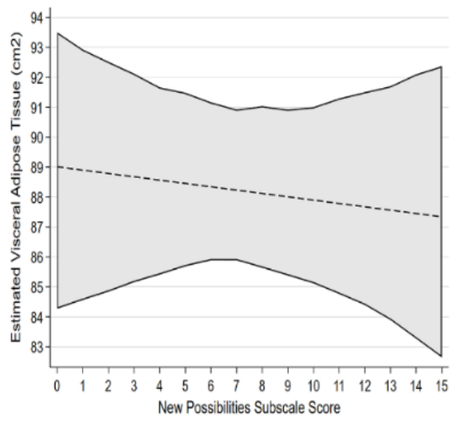
Spiritual Change





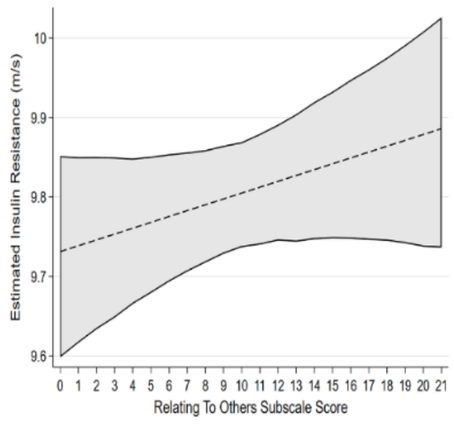


New possibilities



Personal Strength

Relating to Others



Appreication of life