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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

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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 *ArmeD SerVices TrAuma and RehabilitatioN OutComE* (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 (protocol no:357/PPE/12) agreed 15 January 2013. Its results will be disseminated through manuscripts in clinical/academic journals and presentations at professional conferences, and through participant and stakeholder communications.

Trial registration number The ADVANCE Study is registered at ISRCTN ID: ISRCTN57285353.

Strengths and limitations of this study

► *ArmeD SerVices TrAuma and RehabilitatioN OutComE* (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 5 and 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; they are frequently termed 'unexpected survivors'.[2] Rehabilitation took place at the Defence Medical Rehabilitation Centre (DMRC) 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 focused 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] While this evidence suggests battlefield-injured ex-personnel or serving personnel are at higher risk of CVD, the strength of evidence is low,[14 18 50] and the only UK data[36] challenge these 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 (eg, 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 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 MSK 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
Among 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% to 46% for depression and 16% to 36% for anxiety disorders (excluding post-traumatic stress disorder (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% to 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 is largely unknown, particularly in combat casualties.

Hypotheses and objectives
The objective of the *ArmeD* Ser*V*ices Tr*A*uma Rehabili-tatio*N* Out*Com*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 with 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

Box 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 cardiovascular disease (previous stroke or transient ischaemic attack, ischaemic heart disease, peripheral vascular disease) prior to injury/deployment of interest
► 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 2two 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 >38°C or <36°C
  – Heart rate >90 beats/min
  – Respiratory rate >20 breaths/min participants suffering from an acute infection will be excluded initially but will be reapproached to take part once the infection resolves.
► Comparison group only: subsequent combat injury sustained while 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
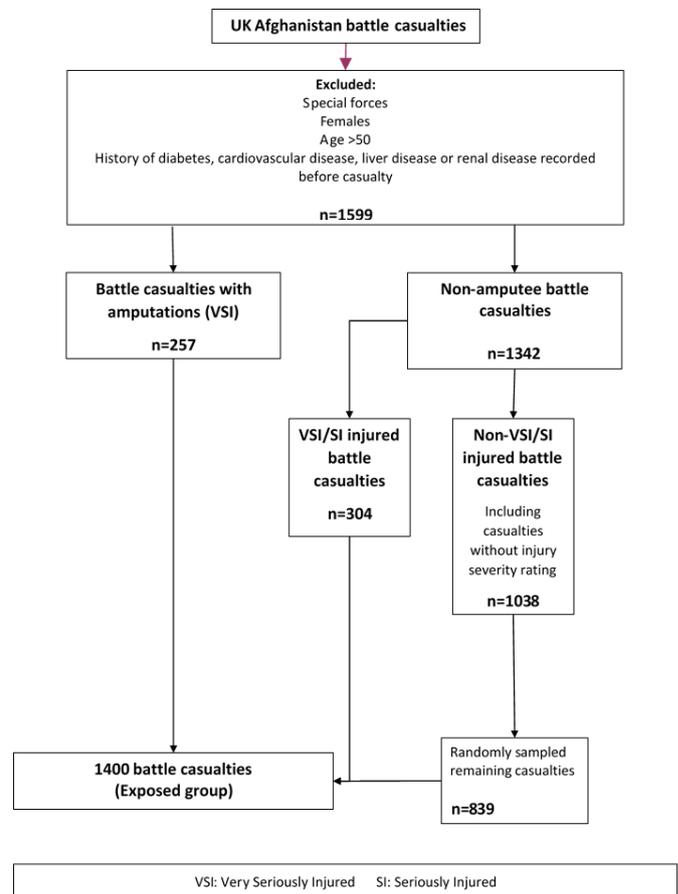

Figure 1 Sampling flow chart for injured personnel.

matched unexposed comparison group (n=600) of males without combat injury will be 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 box 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 was 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; the Defence Patient Tracking System; the Defence Medical Information Capability Programme; the 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.

Setting
Data is collected during a 1day study visit to the DMRC 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 (8hours); 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 National Health Service and Ministry of Defence medical records and for required data linkages to be conducted.
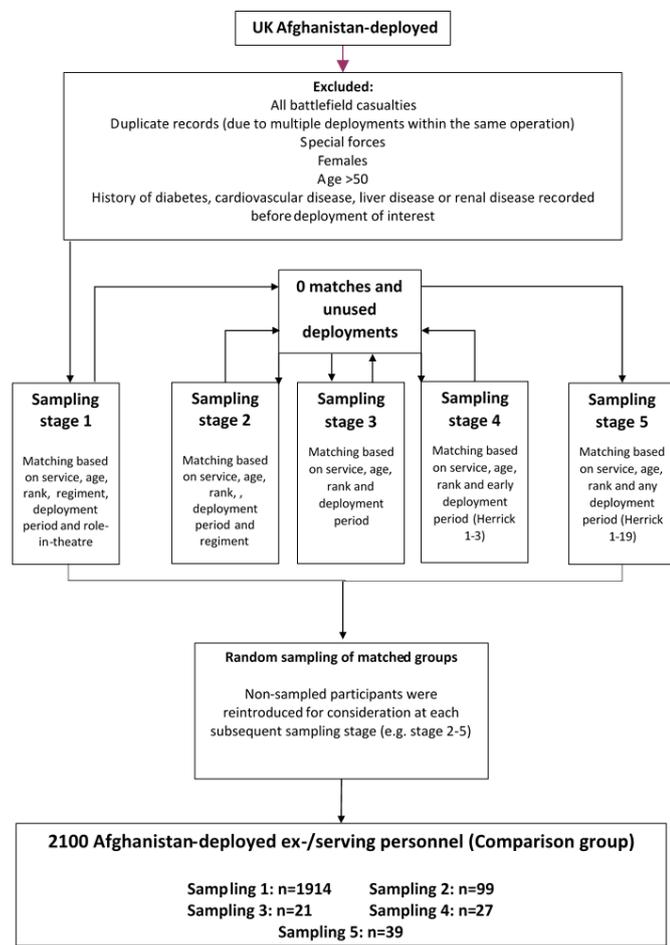
Figure 2 Sampling flow chart for comparison personnel.

Outcome and confounder variables

Core outcome variables collected at baseline are detailed below. These may expand throughout the 20-year duration of the study.
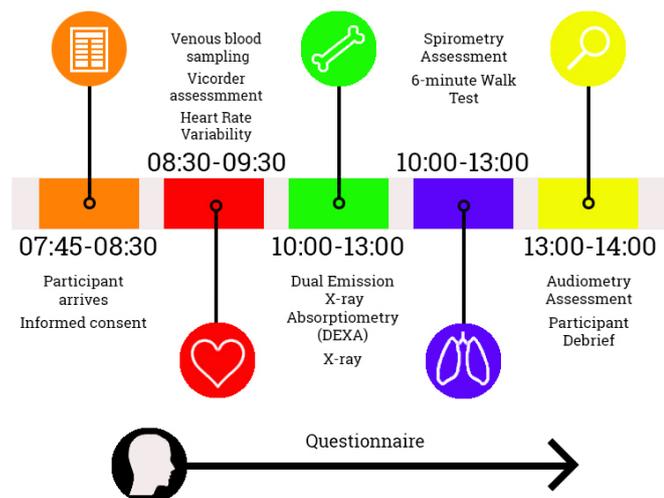
Figure 3 Timeline of ArmeD SerVices TrAuma RehabilitatioN OutComE study day.

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 ischaemic 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 recognised and validated in cardiovascular outcome research.[74–81] Each participant will be flagged with the National Health Service Central Register 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 preinjury 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. Body mass index is calculated using an adjusted formula for amputees (Tzamaloukas et al., 1994).[82]

Vicorder assessment

The Vicorder (Skidmore Medical Limited, Bristol, UK) is a validated device that measures arterial PWV and complex pulse wave form analysis (PWA).[83–85] 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.[84] Using the PWA, the Vicorder also provides a non-invasive measure of peripheral and central blood pressure and arterial central and peripheral augmentation index.[83] Its measurement of PWV has been shown to have a within-subject coefficient of variation of 2.8%.[85] The central and peripheral measurements of arterial stiffness have been shown to be independent predictors of CVD risk.[86]

The assessment takes place on a hospital bed at a 30° 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 PWV. 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

Cardiac interbeat intervals for the measurement of HRV is undertaken using an ECG device (Mega Motion Faros 180 recorder; Mega, Finland). Two consecutive 5 min recordings

of ECG-derived cardiac interbeat intervals will be obtained using spontaneous breathing followed by a 5 min paced breathing exercise, both in a supine position.[87 88] Tests are completed in a noise and temperature-controlled environment. Measures of HRV are undertaken offline using the recorded cardiac interbeat data.

Serum samples
Venous blood is drawn and analysed for full blood count, lipids, glucose, liver function, urea and electrolytes, Haemaglobin A1c (HbA1c) and HsCRP (online supplemental materials 1).

QRISK
10-year cardiovascular risk will be determined using the QRISK calculator[89] 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 nose-clips, 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[90] and post-concussive symptoms are assessed using Participant Reported Outcome Measures (PROMS)[91] (table 1).

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 semiflexed position (7–10°) using the Synaflexer frame are performed as per recommendations for the assessment of osteoarthritis.[92–95] Anterior–lateral and skyline views (inferior–superior) of the patellofemoral joint with the knees in 30° of flexion are taken.[95 96] Hips are also assessed radiographically with an AP pelvis film (focal length 100 cm, hips internally rotated 15°).[97] Radiographs are scored according to the Kellgren and Lawrence radiographic osteoarthritis scoring method[98] for both the hip and the tibiofemoral joints of the knee. The patella femoral joint will be scored using the Osteoarthritis Research Society International scoring method.[99] AP pelvis X-rays will also be scored for sacroiliitis via the modified New York score.[100]

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)[101] which has previously been used in a military population.[102 103] 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 min. 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 7 min for each leg. For the lumbar spine, legs are elevated onto a square block and hips flexed at a 70° angle; participants remain in this position for 7 min.

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 6 min walk test, and PROMS (table 1).

The AMP-Q assesses an amputee's ability to complete physical tasks ranging from balance, reach, weight distribution/gait and walking,[104–106] from which a SIGAM mobility grading is assigned. The 6 min walk test evaluates functional capacity by measuring the distance an individual is able to walk over a total of 6 min on a hard, flat surface; it is valid in both the able-bodied and amputees.[107 108] The goal is for the individual to walk as far as possible in 6 min at a self-directed pace with rest as needed as they traverse back and forth along a marked walkway.

PROMS used (table 1) assess prosthetic functioning, including socket comfort[109] and usage of prosthetics. Pain is assessed in specific areas of the body (shoulders, arm, hand,[110 111] back,[112] hip,[113] foot,[114] phantom pain and overall pain[115]) as well as type of pain (eg, neuropathic)[116 117] and effects of pain (eg, pain catastrophising).[118]

Axial spondyloarthritis
The presence of the gene HLA-B27, inflammatory back pain and the spondyloarthritis criteria[119 120] is used to assess the prevalence of spondyloarthritis (axSpA). Inflammatory back pain is assessed using the Assessment of Spondyloarthritis International Society (ASAS) experts' Inflammatory back pain criteria[120] and classification of axSpA through the ASAS classification criteria.[119]

Mental health
Mental health is assessed using PROMS (table 1) investigating adverse childhood events,[121] alcohol and drug use,[122 123] common mental disorders,[124 125] PTSD,[126 127] post-traumatic growth,[128] quality of life[129 130] and social support.[131]

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

Table 1 Patient reported outcome measures: MSK, pain and physical function

	Measure	Questionnaire type	N items
Musculoskeletal disease			
Amputee physical functioning	Amputee Mobility Predictor Questionnaire/ Assessment[104–106]	Clinician assessment	24
	Prosthetic functioning	Self-report	6 (per missing limb)
	Prosthetic Socket Comfort Score[109]		
	Special Interest Group in Amputee Medicine[134]	Clinician assessment	12
Pain	Brief Pain Inventory-Short Form[115]	Self-report	15
	Disability Arm, Shoulder and Hand Questionnaire[110 111]	Self-report	30
	DN4*[117]	Self-report	7
	Knee Osteoarthritis Outcomes Score[135 136]	Self-report	42
	Manchester-Oxford Foot Questionnaire[114]	Self-report	16
	Neuropathic Pain Symptom Inventory[116]	Self-report	12
	Non-Arthritic Hip Score[113]	Self-report	20
	Oswestry Disability Index[112]	Self-report	10
	Pain Catastrophising Scale[118]	Self-report	13
Physical fitness	International Physical Activity Questionnaire[137]	Self-report	20
Mental health			
Alcohol and drug use	Alcohol Use Disorder Identification Toolkit[122]	Self-report	10
	Drug Use Disorder Identification Toolkit[123]	Self-report	11
Common mental disorders	Generalised Anxiety Disorder-7[124]	Self-report	7
	Patient Health Questionnaire-9[125]	Self-report	9
Post-traumatic growth	Deployment-related Post-Traumatic Growth Inventory*[128]	Self-report	21
Post-traumatic stress disorder	Post Traumatic Check List-Civilian[126]	Self-report	17
	Post Traumatic Check List-DSM V[127]	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*[121]	Self-report	12
Mild/traumatic brain injury	Ohio-State University Traumatic Brain Injury Identification Method Questionnaire[90]	Clinician Interview	13
	Rivermead Post-Concussion Questionnaire[91]	Self-report	18
Quality of life	Arizona Sexual Experiences Scale[130]	Self-report	5
	EQ-5D-5L[129]	Self-report	
Social support	Multidimensional Perceived Social Support Questionnaire[131]	Self-report	12

*Adapted versions.
MSK, musculoskeletal.

data (eg, 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.[37 71 73]

Bio-sample storage and other serum samples

Approximately 20 mL of blood (whole blood/plasma/serum/DNA [dried whole blood spots stored on Whatman FTA cards]) and 50 mL of urine are stored at −80°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, luteinising hormone and sex hormone binding globulin 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 V.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 (HR of ≥1.70) among those with traumatic injury compared with 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 ≥10% at 20 years is expected in the comparison group with a HR of ≥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 HR of ≥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 PWV, 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 with 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 χ^2 or Fisher's exact test where appropriate. T-tests and one-way analysis of variance 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. Generalised 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 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 while 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 V.16 (Stata Corp) 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 approval (protocol no: 357/PPE/12), granted on 15 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.

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	BASELINE	FOLLOW UP APPOINTMENTS
CARDIOVASCULAR RISK/DISEASE		
BLOOD PRESSURE	x	x
-DIASTOLIC		
-SYSTOLIC		
HEART RATE VARIABILITY		x
-PACED BREATING		
-SPONTANEOUS BREATING		
MAJOR ADVERSE CARDIOVASCULAR ENDPOINT (MACE) & INDIVIDUAL COMPONENTS OF THE PRIMARY COMPOSITE CVD SCORE	x	x
QRISK	x	x
SERUM SAMPLES	x	x
-ALANINE AMINOTRANSFERASE		
-ALBUMIN		
-ALKALINE PHOSPHATASE		
-BASOPHILS		
-BILIRUBIN		
-CHOLESTEROL		
-EOSINOPHILS		
-FASTING GLUCOSE		
-GAMMA-GLUTAMYL TRANSPEPTIDASE		
-HBA1C		
-HEMOGLOBIN		
-HIGH DENSITY LIPOPROTEINS		
-HIGH DENSITY LIPOPROTEIN/CHOLESTEROL RATIO		
-HIGH SENSITVITY C-REACTIVE PROTEIN		
-LOW DENSITY LIPOPROTEINS		
-LYMPHOCYTES		
-NEUTROPHILS		
-NON-HIGH DENSITY LIPOPROTEIN CHOLESTEROL		
-PLATELET		
-TRIGLYCERIDES		
-WHITE BLOOD CELLS		
SMOKING/TOBACCO USE	x	x

	BASELINE	FOLLOW UP APPOINTMENTS
-CURRENT/PAST SMOKING HABITS		
-NICOTINE REPLACEMENT THERAPY		
UREA & ELECTROLYTES	x	x
-CREATININE		
-ESTIMATED GLOMERULAR FILTRATION RATE		
-POTASSIUM		
-SODIUM		
-UREA		
VICORDER ASSESSMENT	x	x
-AUGMENTATION INDEX		
-CENTRAL BLOOD PRESSURE		
-PULSE WAVE ANALYSIS		
-PULSE WAVE VELOCITY		
WHATMAN CARD	x	
CARDIORESPIRATORY		
SPIROMETRY	x	x
-FORCED EXPIRATORY VOLUME		
-FORCED VITAL CAPACITY		
MUSCULOSKELETAL DISEASE		
AMPUTEE MOBILITY PREDICTOR QUESTIONNAIRE*	x	x
AXIAL SPONDYLOARTHRITIS	x	x
-ASSESSMENT OF SPONDYLOARTHRITIS INTERATIONAL SOCIETY CRITERIA		
-FEATURES OF SPONDYLOARTHRITIS		
BRIEF PAIN INVENTORY-SHORT FORM		x
DISABILITY ARM, SHOULDER AND HAND QUESTIONNAIRE	x	x
KNEE OSTEOARTHRITIS OUTCOMES SCORE	x	x
MANCHESTER-OXFORD FOOT QUESTIONNAIRE		x
NEUROPATHIC PAIN: DN4		x
NEUROPATHIC PAIN SYMPTOM INVENTORY		x
NON-ARTHRITIC HIP SCORE	x	x
OSWESTRY DISAIBLITY INDEX	x	x

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	BASELINE	FOLLOW UP APPOINTMENTS
PAIN CATASTROPHISING SCALE		x
PHANTOM/STUMP PAIN*	x	x
PHYSICAL FUNCTION	x	x
PROSTHETICS OUTCOMES*	x	x
RADIOLOGY	x	x
* - DUAL EMISSION X-RAY ABSORPTIOMETRY*		
* -X-RAY*		
SIX-MINUTE WALK TEST	x	x
* -DISTANCE TRAVELLED*		
* -PULSE VARIATION*		
MENTAL HEALTH		
ALCOHOL USE DISORDER IDENTIFICATION TOOLKIT	x	x
DRUG USE DISORDER IDENTIFICATION TOOLKIT		x
DEPLOYMENT-RELATED POST-TRAUMATIC GROWTH INVENTORY	x	x
POST-TRAUMATIC CHECK LIST-CIVILIAN	x	
POST-TRAUMATIC CHECK LIST V		x
PATIENT HEALTH QUESTIONNAIRE-9	x	x
GENERALISED ANXIETY DISORDER-7	x	x
OTHER		
AUDIOMETRY	x	x
BIOMETRIC ASSESSMENT	x	x
* -BMI*		
* -HEIGHT*		
* -WAIST/HIP RATIO*		
* -WEIGHT*		
CHILDHOOD ADVERSE EVENTS	x	x
FAMILY HISTORY	x	x
* -CANCER*		
* - CARDIOVASCULAR DISEASE*		
* -MENTAL HEALTH*		
HORMONE PROFILE		x
* -TESTOSTERONE*		
* -SEX HORMONE BINDING GLOBULIN*		

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	BASELINE	FOLLOW UP APPOINTMENTS
-FOLLICULAR STIMULATING HORMONE		
-LUTEINIZING HORMONE		
INSOMNIA SEVERITY INDEX/PITTSBURGH SLEEP QUALITY INDEX	x	x
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE	x	x
OHIO-STATE TRAUMATIC BRAIN INJURY IDENTIFICATION QUESTIONNAIRE/ RIVERMEAD POST-CONCUSSIVE QUESTIONNAIRE		x
MEDICAL HISTORY	x	x
-CARDIOVASCULAR DISEASE		
-CARDIORESPIRATORY		
-GASTROINTESTINAL		
-GENITOURINARY		
-MENTAL HEALTH		
-MUSCULOSKELETAL		
-NEUROLOGICAL		
-OTHER		
CURRENT MEDICATION USE	x	x
MILITARY EXPERIENCES	x	x
-DEPLOYMENT HISTORY		
-LENGTH OF SERVICE		
-MILITARY TRAINING		
-MILITARY PRIMARY ROLE		
-RANK		
-VETERAN STATUS		
SOCIODEMOGRAPHIC	x	x
-ETHNICITY		
-RELATIONSHIP STATUS		
-EMPLOYMENT STATUS		
TRAUMA DETAILS (EXPOSED GROUP ONLY)	x	
-ABBREVIATED INJURY SCORE		
-BODY REGION		
-CAUSE OF INJURY		
-NEW INJURY SEVERITY SCORE		

* *AMPUTEE SPECIFIC OUTCOMES*

	BASELINE	FOLLOW UP APPOINTMENTS
CARDIOVASCULAR RISK/DISEASE		
BLOOD PRESSURE	x	x
-DIASTOLIC		
-SYSTOLIC		
HEART RATE VARIABILITY		x
-PACED BREATING		
-SPONTANEOUS BREATING		
MAJOR ADVERSE CARDIOVASCULAR ENDPOINT (MACE) & INDIVIDUAL COMPONENTS OF THE PRIMARY COMPOSITE CVD SCORE	x	x
QRISK	x	x
SERUM SAMPLES	x	x
-ALANINE AMINOTRANSFERASE		
-ALBUMIN		
-ALKALINE PHOSPHATASE		
-BASOPHILS		
-BILIRUBIN		
-CHOLESTEROL		
-EOSINOPHILS		
-FASTING GLUCOSE		
-GAMMA-GLUTAMYL TRANSPEPTIDASE		
-HBA1C		
-HEMOGLOBIN		
-HIGH DENSITY LIPOPROTEINS		
-HIGH DENSITY LIPOPROTEIN/CHOLESTEROL RATIO		
-HIGH SENSITVITY C-REACTIVE PROTEIN		
-LOW DENSITY LIPOPROTEINS		
-LYMPHOCYTES		
-NEUTROPHILS		
-NON-HIGH DENSITY LIPOPROTEIN CHOLESTEROL		
-PLATELET		
-TRIGLYCERIDES		
-WHITE BLOOD CELLS		
SMOKING/TOBACCO USE	x	x

	BASELINE	FOLLOW UP APPOINTMENTS
-CURRENT/PAST SMOKING HABITS -NICOTINE REPLACEMENT THERAPY		
UREA & ELECTROLYTES -CREATININE -ESTIMATED GLOMERULAR FILTRATION RATE -POTASSIUM -SODIUM -UREA	X	X
VICORDER ASSESSMENT -AUGMENTATION INDEX -CENTRAL BLOOD PRESSURE -PULSE WAVE ANALYSIS -PULSE WAVE VELOCITY	X	X
WHATMAN CARD	X	
CARDIORESPIRATORY		
SPIROMETRY -FORCED EXPIRATORY VOLUME -FORCED VITAL CAPACITY	X	X
MUSCULOSKELETAL DISEASE		
AMPUTEE MOBILITY PREDICTOR QUESTIONNAIRE*	X	X
AXIAL SPONDYLOARTHRITIS -ASSESSMENT OF SPONDYLOARTHRITIS INTERATIONAL SOCIETY CRITERIA -FEATURES OF SPONDYLOARTHRITIS	X	X
BRIEF PAIN INVENTORY-SHORT FORM		X
DISABILITY ARM, SHOULDER AND HAND QUESTIONNAIRE	X	X
KNEE OSTEOARTHRITIS OUTCOMES SCORE	X	X
MANCHESTER-OXFORD FOOT QUESTIONNAIRE		X
NEUROPATHIC PAIN: DN4		X
NEUROPATHIC PAIN SYMPTOM INVENTORY		X
NON-ARTHRITIC HIP SCORE	X	X
OSWESTRY DISAIBLITY INDEX	X	X

	BASELINE	FOLLOW UP APPOINTMENTS
PAIN CATASTROPHISING SCALE		x
*PHANTOM/STUMP PAIN**	x	x
PHYSICAL FUNCTION	x	x
*PROSTHETICS OUTCOMES**	x	x
RADIOLOGY	x	x
- DUAL EMISSION X-RAY ABSORPTIOMETRY		
-X-RAY		
SIX-MINUTE WALK TEST	x	x
-DISTANCE TRAVELLED		
-PULSE VARIATION		
MENTAL HEALTH		
ALCOHOL USE DISORDER IDENTIFICATION TOOLKIT	x	x
DRUG USE DISORDER IDENTIFICATION TOOLKIT		x
DEPLOYMENT-RELATED POST-TRAUMATIC GROWTH INVENTORY	x	x
POST-TRAUMATIC CHECK LIST-CIVILIAN	x	
POST-TRAUMATIC CHECK LIST V		x
PATIENT HEALTH QUESTIONNAIRE-9	x	x
GENERALISED ANXIETY DISORDER-7	x	x
OTHER		
AUDIOMETRY	x	x
BIOMETRIC ASSESSMENT	x	x
-BMI		
-HEIGHT		
-WAIST/HIP RATIO		
-WEIGHT		
CHILDHOOD ADVERSE EVENTS	x	x
FAMILY HISTORY	x	x
-CANCER		
- CARDIOVASCULAR DISEASE		
-MENTAL HEALTH		
HORMONE PROFILE		x
-TESTOSTERONE		
-SEX HORMONE BINDING GLOBULIN		

Supplemental material

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	BASELINE	FOLLOW UP APPOINTMENTS
-FOLLICULAR STIMULATING HORMONE		
-LUTEINIZING HORMONE		
INSOMNIA SEVERITY INDEX/PITTSBURGH SLEEP QUALITY INDEX	X	X
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE	X	X
OHIO-STATE TRAUMATIC BRAIN INJURY IDENTIFICATION QUESTIONNAIRE/ RIVERMEAD POST-CONCUSSIVE QUESTIONNAIRE		X
MEDICAL HISTORY	X	X
-CARDIOVASCULAR DISEASE		
-CARDIORESPIRATORY		
-GASTROINTESTINAL		
-GENITOURINARY		
-MENTAL HEALTH		
-MUSCULOSKELETAL		
-NEUROLOGICAL		
-OTHER		
CURRENT MEDICATION USE	X	X
MILITARY EXPERIENCES	X	X
-DEPLOYMENT HISTORY		
-LENGTH OF SERVICE		
-MILITARY TRAINING		
-MILITARY PRIMARY ROLE		
-RANK		
-VETERAN STATUS		
SOCIODEMOGRAPHIC	X	X
-ETHNICITY		
-RELATIONSHIP STATUS		
-EMPLOYMENT STATUS		
TRAUMA DETAILS (EXPOSED GROUP ONLY)	X	
-ABBREVIATED INJURY SCORE		
-BODY REGION		
-CAUSE OF INJURY		
-NEW INJURY SEVERITY SCORE		
* *AMPUTEE SPECIFIC OUTCOMES*		