Forever wounds of the forever war

Ian J Stewart

Given the prolonged duration of the conflict in Afghanistan, and the nebulous criteria for success, it has been termed the 'Forever War'. On 30 August 2021, after almost 20 years of conflict, the Forever War finally came to an end when the last US forces left the country. In the field of combat casualty care, this is a time for reflection. Without question, the medical care provided to casualties in Iraq and Afghanistan was unparalleled. Advances in trauma coupled with rapid evacuation to medical facilities capable of damage control resuscitation and surgery resulted in the lowest case fatality rate in the history of warfare. While this is rightly considered a great success, we cannot end our inquiry with a short-term survival outcome. Clearly, the trajectories of these people's lives have been forever and inexorably altered. Now that the Forever War has come to an end, it is time to systematically examine the long-term consequences of combat injury.

LONG-TERM COMPLICATIONS OF COMBAT INJURY

Preliminary evidence from retrospective studies has found that combat injury is associated with a wide variety of poor long-term health outcomes, including cardiovascular disease (CVD), hypertension and diabetes.[1] Additionally, combat injury has been associated with adverse mental health outcomes, such as post-traumatic stress disorder (PTSD), anxiety and depression.[2] The implications of this work are clear: for Veterans injured in combat, the Forever War continues.

While retrospective studies are sufficient to generate hypotheses, they are inadequate for a systematic examination of the long-term consequences of combat injury for several reasons. First, patients with a history of combat injury may seek more care and thus see clinicians more often than their non-injured counterparts. This could lead to ascertainment bias. Second, the relationship between combat injury and poor outcomes such as CVD is likely to be complex. For example, combat-injured patients are more likely to develop PTSD,[2] which has in turn been associated with an increased risk of CVD.[3] Robust, prospective data collection is needed to define these potential confounding variables and competing risks. Lastly, retrospective studies do not lend themselves to studying underlying mechanisms, which could define important pathways and suggest potential treatment options. Given these limitations, a large, prospective, observational study is needed to advance the field.

A BREAKTHROUGH ADVANCE

The Armed Services Trauma Rehabilitation Outcome (ADVANCE) study is a prospective, observational cohort of combat-injured service members and matched controls.[4] The study subjects will be longitudinally followed for 20 years. The primary outcome of ADVANCE is the incidence of major adverse cardiovascular events (MACE), defined as a composite of CVD death, non-fatal myocardial infarction, non-fatal stroke and revascularisation procedures. In addition, ADVANCE will evaluate respiratory function, musculoskeletal disease, physical function, pain, mental health and socioeconomic outcomes. By prospectively following combat casualties along with an appropriate control group, ADVANCE will be able to elucidate the association between combat injury and poor long-term outcomes. By collecting data on potentially confounding variables and longitudinally collecting bio-samples, the study design will also allow for mechanistic studies, which could explain the underlying pathogenesis by which combat injury increases the subsequent risk of CVD.

Boos *et al* present the baseline findings from the ADVANCE study.[5] The study examined 579 male combat casualties that were injured in Afghanistan from 2003 to 2014 and compared them with 565 controls matched by age, service, rank, regiment, deployment period and role. The study examined cardiovascular risk based on metabolic syndrome and central augmentation index (a marker of endothelial dysfunction). Injured subjects were more likely to have metabolic syndrome (18.0%) compared with uninjured subjects (11.8%). While there is the possibility of residual confounding, these findings remained significant after adjustment for age, time from injury, physical activity, ethnicity and rank. The mean central augmentation index was also higher in injured subjects, a difference that remained significant after adjustment. Furthermore, there was evidence of a dose-response, where more severely injured patients were more likely to develop metabolic syndrome and had higher central augmentation indexes. Given that the average age of ADVANCE participants was 34.1 years, MACE events are likely to be rare. However, these findings suggest that as injured subjects age, they will be at higher risk for CVD compared with subjects that were not injured.

HOW DOES COMBAT INJURY INCREASE RISK?

While there is insufficient evidence to explain the association between combat injury and poor long-term health outcomes such as CVD, it has been hypothesised to be a result of complex interplay between a variety of factors (figure 1). The first potential pathway is inflammation. Trauma induces a brisk inflammatory response which may alter the host immune system resulting in chronic inflammation.

While there is a paucity of evidence regarding the long-term impact of trauma in general on inflammation, there is some evidence from two specific types of trauma: burn injury and traumatic brain injury (TBI). A study of 997 paediatric burn patients found that cytokine levels were elevated for up to 3 years compared with controls.[6] Similar results were seen in a study that examined 207 subjects with mild TBI. This study found that a variety of inflammatory biomarkers were elevated compared with controls for up to 12 months after injury.[7] Chronic inflammation has in turn been associated with adverse physical health outcomes such as CVD.[8] Notably, high-sensitivity C reactive protein, a well-established inflammatory marker for CVD risk, was higher in the injured cohort in ADVANCE. The second potential pathway is through adverse mental health outcomes, including PTSD which has been associated with CVD.[3] While the present study did not examine the potential role for mental health outcomes on cardiovascular risk in the ADVANCE population, these data are being collected and will likely be a subject of future investigations. The third pathway by which combat injury may increase risk is via behavioural changes, such as decreased physical activity, weight gain, substance abuse and sleep disturbances (such as insomnia). Here again, the ADVANCE study provides some evidence

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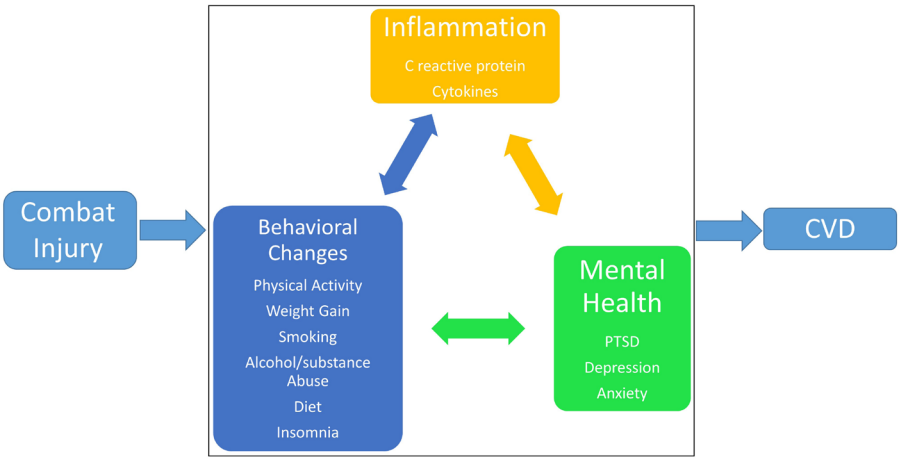

Figure 1 Hypothesised pathways by which combat injury may result in poor long-term health outcomes. CVD, cardiovascular disease; PTSD, post-traumatic stress disorder.

with less physical activity, shorter 6 min walk distances and larger waist circumferences seen in combat-injured patients. Lastly, it should be noted that these pathways are inter-related and not mutually exclusive. For example, both PTSD[9] and obesity[10] have been associated with chronic inflammation. Further analysis of the ADVANCE cohort will better define the relative contributions of these potential pathways.

THE NEXT ADVANCE

While ADVANCE is an important step forward in understanding the long-term impact of an episode of combat trauma, it will leave some questions unanswered. First, the cohort is restricted to male service members. What will the impact of combat injury be on female service members? While casualty rates for women were low in Afghanistan, given the increasing number of women in combat roles they will likely compose a greater proportion of combat casualties in future conflicts. Second, the injured populations of the UK and the USA are different. Will differences in access to care, socioeconomics and race/ethnicity modify the relationship between combat injury and subsequent cardiovascular risk? Lastly, and perhaps most importantly, what interventions can be made to mitigate complications and improve long-term outcomes for wounded service members? We owe it to these young men and women, every one of them a volunteer, who have sacrificed so much for our nations, to answer these questions.

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